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CHAPTER 01 GASTRO-INTESTINAL SYSTEM

01.01 DYSPEPSIA AND GASTRO-OESOPHAGEAL REFLUX DISEASE

DYSPEPSIA
Pain or discomfort (including fullness, early satiety, bloating or nausea) centered in the upper abdomen. Functional (non-ulcer) dyspepsia is a condition where investigation of dyspepsia has not identified an underlying organic disease.

Before starting treatment
Consider stopping, replacing or adjusting regimen of causative drug, e.g. NSAIDs, bisphosphonates, tetracycline's, calcium channel blockers, if possible.
Refer patients >50 years with new-onset symptoms, and all patients with alarm symptoms (e.g. anaemia, dysphagia, evidence of bleeding, weight loss, recurrent vomiting) for endoscopy.
Distinguish gastro-oesophageal reflux disease from other causes of dyspepsia.
Avoiding specific foods and changing lifestyle (e.g. low fat diet, avoidance of coffee and alcohol, weight loss and stopping smoking) may help.

Drug choice
Drug treatment has a low success rate; reassurance and explanation are the keys to management. If acid suppression is required, avoid long term continuous treatment; use intermittent short courses of treatment as needed.

Antacids
'When required' use may be appropriate in some patients with dyspepsia but antacids appear to be no better than placebo in functional dyspepsia (where placebo response is 20–60%).

H. pylori eradication
Dyspepsia: consider the 'test and treat' strategy: perform a non-invasive H. pylori test, eradicate the infection in those testing positive and give symptomatic treatment to those testing negative.
Functional dyspepsia: eradication cures symptoms in a minority of cases (similar to any other treatment for functional dyspepsia) and appears to be cost effective. See Table 01.01 Recommended H. pylori eradication regimens.

Acid suppression
Dyspepsia: PPIs are more effective than antacids or H2 antagonists at reducing symptoms; try full dose PPI for 4 weeks.
Functional dyspepsia: try either a H2 antagonist or PPI for 4 weeks (approximately 10% of patients benefit over placebo). As there is no evidence of any difference in effectiveness between the 2 classes, consider an H2 antagonist as it is less expensive.

Other drug treatment
At present, there is insufficient evidence regarding the value of domperidone and metoclopramide in functional dyspepsia. Other options include low dose TCAs, antispasmodic agents, sucralfate, behavioural therapy or psychotherapy, but none is of proven benefit.

Length of treatment
If the patient fails to respond after 4 weeks of acid suppression, consider increasing the dose of acid suppressant or switching drug classes for a further 4 weeks.
Refer to a specialist people whose symptoms persist after:

- confirmed eradication of H. pylori
- 8 weeks of acid suppressant treatment.

GASTRO-OESOPHAGEAL REFLUX DISEASE
A chronic and relapsing condition where exposure of the oesophagus to refluxed gastric contents causes symptoms (such as heartburn and acid regurgitation) or mucosal damage (oesophagitis). Symptom severity correlates poorly with the degree of mucosal damage.

Rationale for drug use:
Relieve symptoms and improve quality of life., Heal oesophagitis. Reduce risk of complications.

Before starting treatment
Lifestyle changes (see Dyspepsia) may be useful and should be recommended, although evidence for their effectiveness in GORD is limited.
Other suggestions include eating smaller meals, not eating before bed, raising the head of the bed and avoiding tight clothing.

Where possible stop drugs (e.g. NSAIDs, calcium channel blockers, nitrates and theophylline) known to cause or worsen reflux.

Endoscopy is indicated for:
- alarm symptoms (including dysphagia, weight loss, bleeding, abdominal mass, anaemia).
- symptoms which are atypical or refractory to initial treatment
- longstanding symptoms in those >45–55 years who may be at risk of complications.

Treatment is often empiric as most patients with GORD have no endoscopic evidence of the disease.

**Drug choice**

Antacids: more effective than placebo in the relief of daytime symptoms. Use often limited by their short duration of action.

H₂ antagonists: provide adequate symptom relief and healing for many patients with mild-to-moderate GORD.

PPIs: faster and more effective than H₂ antagonists in controlling symptoms and healing inflammation, regardless of disease severity. All PPIs are clinically equivalent for most patients.

Metoclopramide and domperidone: may be useful in some patients with dyspeptic symptoms (e.g. bloating or early satiety) as well as reflux. They are as effective as H₂ antagonists in relieving symptoms, but do not heal oesophagitis.

**Treatment regimens**

Use a graduated approach, depending on symptom severity.

**Mild, intermittent symptoms**

Patient or pharmacist directed therapy: lifestyle measures and antacids (short intermittent courses of H₂ antagonist may be considered).

**Mild-to-moderate symptoms**

Prescriber directed therapy: depending on symptom severity choose

'Step-down': start with a PPI, then use minimum dose of PPI required to control symptoms or a less potent agent once symptoms are controlled.

'Step-up': lifestyle measures and antacids, then H₂ antagonists, followed by PPIs if necessary.

**Moderate-to-severe symptoms**

Use the 'step-down' approach for rapid control of symptoms, confirmation of diagnosis and healing of oesophagitis. Refer those with refractory or complicated disease to a specialist.

**Length of treatment**

For endoscopically-determined severe oesophagitis or complicated disease (e.g. stricture formation, Barrett's oesophagus) continue regular PPI long term.

In other people with symptomatic improvement, continue treatment for 4 weeks at the same dose. Consider stopping treatment after the initial course; a significant minority will not relapse.

In those who relapse consider endoscopy (if not done earlier) or repeat the course of previously successful drug, followed by 'step-down' to intermittent, symptom-driven treatment with the least costly but effective regimen.

**Treatment endpoints**

For people with complications, such as stricture or bleeding from oesophagitis, confirmation of healing is required; otherwise it is unnecessary.

**H. pylori and GORD**

There is no consistent evidence of an association between H. pylori and GORD.

However, it is recommended that H. pylori is tested for and eradicated in patients with GORD who require long term PPI treatment. This is because profound acid suppression may accelerate the progression of H. pylori-induced atrophic gastritis, increasing the potential risk of cancer.

**Infant GORD**

Common, but does not usually require treatment as it resolves with increasing age. If severe, thickening oral fluids may help. H₂ antagonists or PPIs are also used but drug treatment should be avoided if possible; consider referral to a specialist.

**Practice points**

- doubling dose of H₂ antagonist does not increase efficacy and is not appropriate.
- intermittent use of PPIs may be more cost-effective than continuous use of H₂ antagonists
- in most cases combination treatment is less effective than increasing the dose of PPI
- evidence suggests that control of symptoms equates with healing of oesophagitis in patients maintained on PPIs.
Helicobacter pylori-related ulcers
H. pylori infection is the most common cause of peptic ulcer disease (PUD); most other cases are associated with the use of NSAIDs, see NSAID-related ulcers.

Eradication of H. pylori is considered first line treatment for PUD, see Recommended H. pylori eradication regimens (Table 01.01). This confers long term cure in most of those affected by PUD. Other treatments that do not eradicate H. pylori may heal ulcers and prevent relapse, but only while continued.

Delay eradication of H. pylori in acute severe complications of PUD until the person is stabilized.

Rationale for drug use
Heal and reduce relapse rate of duodenal and gastric ulcers caused by H. pylori.
Reduce risk of PUD in patients who are H. pylori positive and at increased risk of NSAID-induced ulcer complications before starting long term NSAID.
Symptomatic relief in functional (non-ulcer) dyspepsia.

Before starting treatment
Confirm the presence of H. pylori by urea breath test, faecal antigen test, laboratory-based serology or biopsy-based methods.

When to start treatment
Confirmed H. pylori infection and:

- acute, recurrent or chronic gastric or duodenal ulcer
- gastric mucosa-associated lymphoid tissue (MALT) lymphoma
- following gastric cancer resection.

Consider eradicating H. pylori in atrophic gastritis, first degree relatives of gastric cancer patients and when treating uncomplicated non-ulcer dyspepsia.

Treatment regimens
Regimens with eradication rates of >80% are recommended. The most consistently effective combination is a PPI with clarithromycin and amoxycillin (see Table 01.01 Recommended H. pylori eradication regimens). Dual therapy and other ad hoc regimens are not recommended because of unsatisfactory eradication rates and the risk of developing drug resistance. True reinfection is uncommon after successful eradication. In patients with refractory infection or who undergo reinfection after therapy, H. pylori is usually antibiotic-resistant.

Factors influencing drug selection
Using at least 2 antibacterials improves eradication rates and reduces the subsequent acquired resistance (especially with metronidazole) associated with partial treatment.

Compliance is influenced by:

- adverse effect profile; all regimens cause nausea, diarrhoea and taste disturbance; adverse effects are more common with metronidazole
- cost to patient (only some available on the PBS)
- duration of treatment (7-day treatments have the lowest rate of treatment withdrawal)
- number of tablets required each day.

The optimal second line regimen when treatment fails is unclear. Ideally, treatment should be guided by sensitivity testing. If this is unavailable, use quadruple therapy (see Table 01.01 Recommended H. pylori eradication regimens) or PPI-based triple therapy using different antibacterial combination to initial regimen.

Microbiological culture and antibiotic sensitivity tests are indicated when 2 courses fail.

Treatment endpoints
Eradication is defined as testing negative for the organism 4 weeks or longer after eradication therapy, and at least 2–4 weeks after stopping acid suppressant treatment to avoid a false-negative result.

Confirmation of H. pylori eradication is generally advisable but not always necessary (varies according to factors such as initial indication and availability of investigations).

If indicated, use either the urea breath test or endoscopy (particularly for gastric ulcers and complicated duodenal ulcers, e.g. bleeding or perforation).

Serology is not a valid method for confirming eradication as antibody levels can take up to a year to fall.

Continue maintenance acid suppressant treatment in those with gastric ulcers, large ulcers (>1 cm diameter) or complicated ulcer disease until healing has been confirmed by endoscopy. Confirm bacterial eradication after stopping acid suppressant treatment.

Long term maintenance acid suppressant treatment may be necessary if eradication treatment fails or is contraindicated and if peptic ulcer recurs even in the absence of reinfection.

Gastric cancer
H. pylori is a recognized risk factor for gastric cancer. Eradication may reduce the risk of cancer at least in the short term; there is not enough evidence to recommend screening and treating the asymptomatic general population for infection (other than in areas of high gastric cancer prevalence).

**Practice points**
- antacids may provide rapid symptomatic relief, but healing is limited
- asymptomatic H. pylori infection does not require treatment
- poor compliance and antibiotic resistance are major causes of failure to eradicate H. pylori; inform patients about possible unpleasant (but not serious) adverse effects, the need for compliance and the possibility of a cure without the need for long term medication

**NSAID-RELATED ULCERS**
Most peptic ulcers induced by NSAIDs (including aspirin) are gastric; they are often silent and present with a complication. H. pylori infection and NSAIDs appear to be independent risk factors for peptic ulcer and peptic ulcer bleeding, see Helicobacter pylori-related ulcers.

**Rationale for drug use**
Heal ulcer to provide symptom control and to reduce risk of complications (e.g. bleeding, perforation, obstruction).

**Before starting treatment**
Test for H. pylori using urea breath test, faecal antigen test, laboratory-based serology or biopsy-based methods.

**Treatment**
Stop the NSAID if possible and substitute simple analgesics (see Paracetamol) and non-drug treatment. Then use H$_2$ antagonist or PPI for 4–8 weeks.
If the NSAID cannot be stopped, healing is slower and recurrence more likely. Use PPI or misoprostol (although misoprostol is not always well tolerated).
After treatment, follow-up endoscopy to confirm healing is advisable.
Eradication of H. pylori infection is recommended after the ulcer has healed, see Recommended H. pylori eradication regimens (Table 01.01).

**Prevention**
PPI, double dose H$_2$ antagonist and misoprostol are all effective for primary and secondary prevention. Continue for duration of NSAID treatment.
PPIs at standard doses are cheaper and more convenient (once daily dosing) than double dose H$_2$ antagonist.
Misoprostol 400 micrograms daily has fewer adverse effects than 800 micrograms daily but is less effective in preventing gastric ulcers.

**Practice points**
- in patients who continue to take NSAIDs, H. pylori eradication followed by acid suppression does not enhance ulcer healing compared with acid suppression alone; however, its eradication is recommended to eliminate it as a potential cause of ulcers.

**01.01.01 Anti-acids and Dimethicone**
Other agents such as alginate acid and simethicone are often included in antacid preparations. Claims are made that these agents help relieve symptoms of reflux or excess gas, but there is limited evidence to support this.

**Mode of action**
Neutralize hydrochloric acid secreted by gastric parietal cells.

**Indications:**
Symptomatic relief of:
dyspepsia
peptic ulcer disease (PUD)
gastro-oesophageal reflux disease (GORD)

**Specific considerations**
Constipation exacerbated by antacids containing aluminium and calcium.
Diarrhoea exacerbated by laxative effect of antacids containing magnesium.
Heart failure, chronic renal failure, cirrhosis, and oedema avoid antacids containing sodium; may increase fluid retention.
Renal impairment: Antacids containing aluminium and/or magnesium should not be used as in severe impairment; as accumulation may occur.
Pregnancy: Safe to use as antacids; ADEC category A.

**Patient counselling**
Take between meals or at bedtime when symptoms occur or you expect they might occur.
Tablets should be chewed or sucked before swallowing for the best effect. Antacids can reduce the effect of a number of other medicines taken by mouth. The best way to avoid a problem is to separate taking antacids and other medicines by at least 2 hours.

**Practice points**
- optimum antacid effect is achieved if taken 1–3 hours after meals
- liquid preparations are more effective, but less convenient, than solid preparations

**ALUMINIUM HYDROXIDE**

**Mode of action**
Neutralize hydrochloric acid secreted by gastric parietal cells.

**Indications**
Symptomatic relief of dyspepsia, peptic ulcer disease and GORD
Phosphate binder in chronic renal failure.

**Specific considerations**
- Constipation: exacerbated by antacids containing aluminium and calcium.
- Diarrhoea: exacerbated by laxative effect of antacids containing magnesium.
- Heart failure, chronic renal failure, cirrhosis, oedema: avoid antacids containing sodium; may increase fluid retention.
- Renal impairment: Aluminium accumulation may result in bone disease and encephalopathy; in severe impairment do not use as an antacid and minimise use as a phosphate binder.
- Surgery: If using as a phosphate binder in renal impairment continue treatment perioperatively.
- Pregnancy: Safe to use as an antacid; contraindicated as a phosphate binder.

**Adverse effects**
Common: constipation
Infrequent: hypophosphataemia
Rare: intestinal obstruction, osteomalacia, proximal myopathy, encephalopathy, anaemia.

**Dosage**
Antacid, dose according to label.
Phosphate binding in renal impairment, 600–1200 mg with food, usually up to 3600 mg (6 tablets) daily.

**Patient counselling**
Phosphate binder: if you skip a meal save your dose and take it when you next eat...

**Practice points**
- relatively slow onset of action as an antacid
- commonly combined with magnesium to prevent constipating effects
- in moderate-to-severe renal impairment monitor plasma aluminium concentrations at baseline and every 3 months
- optimum antacid effect is achieved if taken 1–3 hours after meals
- liquid preparations are more effective, but less convenient, than solid preparations

**Products**
Multi combination products

**MAGNESIUM ANTACIDS**
Agents include magnesium carbonate, magnesium hydroxide and magnesium trisilicate; usually used with aluminium hydroxide. Magnesium hydroxide is the most potent and fastest acting.

**Mode of action**
Neutralize hydrochloric acid secreted by gastric parietal cells.

**Indications**
Symptomatic treatment of dyspepsia, peptic ulcer disease and GORD.

**Adverse effects**
Common: diarrhoea, belching (magnesium carbonate).
Rare: hypermagnesaemia.
Dosage: Dose according to label.
**Products**

ALUMINIUM + MAGNESIUM COMPLEXES SUSP. (ALOXAL®, MAALOX®, MOXAL®, NEUTRACID®, NOVAGEL®)

ALUMINIUM + MAGNESIUM COMPLEXES TABS (ALUMAG®, MALUGEL®, MOXAL®, MAALOX®, NOVAGEL®, RAMCID®)

**SIMETICONE (ACTIVATED DIMETICONE)**

**Mode of action**

Simeticone is a mixture of liquid dimeticones containing finely divided silicon dioxide to enhance the defoaming properties of the silicone. It lowers surface tension and when administered by mouth causes bubbles of gas in the gastrointestinal tract to coalesce, thus aiding their dispersion.

**Indication**

Simeticone is used for the relief of flatulence and abdominal discomfort due to excess gastrointestinal gas in disorders such as dyspepsia and gastro-oesophageal reflux disease.

Simeticone is also used as a defoaming agent in radiography or endoscopy of the gastrointestinal tract.

**Dosage**

Doses of 100 to 250 mg three or four times daily have been given. For many gastrointestinal disorders, it is given with an antacid.

Doses of 20 to 40 mg of simeticone have been given with feeds to relieve colic in infants.

**Practical points**

A brief review of the use of simeticone for gastrointestinal symptoms concluded that although it was commonly prescribed in combination with an antacid, there was no good evidence that it provided additional benefit. When used alone it probably helps to relieve minor postoperative and postprandial symptoms and it was a useful aid in upper gastrointestinal endoscopy. However, some considered there was no convincing evidence that it was effective for the treatment of eructation, flatulence, or other signs or symptoms of excess gastrointestinal gas.

**Products:**

SIMETICONE TABS 120-125 MG (CHEWABLE) (DEFLAT®, GAZIX®)

**01.02 ANTISPASMODICS AND OTHER DRUGS ALTERING GUT MOTILITY**

**NAUSEA AND VOMITING**

**Rationale for drug use:**
Prevent or relieve symptoms.
Prevent complications (dehydration, electrolyte disturbance).

**Before starting treatment**

Identify, treat or remove cause if possible.
Ensure adequate hydration.

**Drug choice**

**Dopamine antagonists**
All except domperidone have central dopamine antagonist activity and may cause EPSE.

Domperidone and metoclopramide are widely used to treat nausea and vomiting. They also have prokinetic activity which may be useful in nausea and vomiting due to gastroparesis.

Prochlorperazine is widely used in the prevention and treatment of nausea and vomiting. It is available as tablets, suppositories or injection.

Droperidol is used for postoperative nausea and vomiting (PONV). It has a long duration of action and counteracts adverse opioid effects; however, the risk of sedation and EPSE limit its use. Although it has been associated with prolongation of QT interval this does not appear clinically important with antiemetic doses.

Haloperidol is used to treat nausea and vomiting following cancer chemotherapy when other agents are ineffective and the risk of adverse CNS effects is considered acceptable.

**Sedating antihistamines**
Dimenhydrinate, pheniramine and promethazine are mainly used to prevent motion sickness and for nausea and vomiting associated with other vestibular disorders. They have additional sedative and anticholinergic properties.

**Anticholinergics**
Hyoscine hydrobromide is used to prevent motion sickness but may be poorly tolerated due to anticholinergic adverse effects.
5HT3 antagonists
Dolasetron, granisetron, ondansetron and tropisetron are mainly used to prevent or treat nausea and vomiting following cancer chemotherapy, radiotherapy or surgery. They appear to have similar efficacy.

Substance P antagonists
Aprepitant is used with a 5HT3 antagonist and dexamethasone to prevent nausea and vomiting associated with highly emetogenic chemotherapy.

Corticosteroids
Dexamethasone is used for prevention of PONV and as adjunctive treatment in chemotherapy-induced nausea and vomiting.

Benzodiazepines
Lorazepam may be used as adjunctive treatment in chemotherapy-induced nausea and vomiting, particularly for anticipatory nausea and vomiting. Efficacy may be related to anxiolytic and sedative effects.

Factors influencing drug selection
The main factor influencing drug selection is the cause of nausea and vomiting. Other factors include:
- Age: the EPSE of dopamine antagonists are more common in children and young adults (usually as acute dystonic reactions) and in the elderly. Age can also influence the risk and severity of nausea and vomiting (e.g. postoperative vomiting is twice as common in children compared to adults).
- Gender: females are more susceptible to nausea and vomiting following cancer chemotherapy, radiotherapy or surgery.
- Route of administration: drugs in rectal or parenteral form are necessary where oral medication is not tolerated or is contraindicated (e.g. after major surgery).
- Severity: in prolonged severe vomiting, high dose combination antiemetic treatment is often needed (seek specialist advice).

Special cases
Cancer chemotherapy
Nausea and vomiting due to chemotherapy can affect quality of life and may result in dehydration, weight loss and malnutrition.

Radiotherapy:
Consider need for prophylaxis with a 5HT3 antagonist and/or dexamethasone. Risk of radiotherapy-induced nausea and vomiting is influenced by the site and dose of radiation as well as individual patient factors.

Pregnancy:
Nausea and vomiting are common during the first trimester. Avoid drug treatment if possible. Emphasize the importance of adequate hydration (e.g. using ice chips if necessary).
Dietary modification may help. Symptoms may also improve with ginger (up to 1 g daily) or pyridoxine (vitamin B6, up to 50 mg twice daily). If these are not effective consider using metoclopramide, promethazine or prochlorperazine orally, if tolerated. Prochlorperazine suppositories are useful if nausea and vomiting are severe. Hyperemesis gravidarum: IV rehydration is the main treatment. Metoclopramide, prochlorperazine or ondansetron are used if symptoms are prolonged and intractable.

Postoperative
Prophylaxis is important and provides the greatest benefit for patients at higher risk of PONV. There is no one treatment of choice; 5HT3 antagonists, droperidol, dexamethasone, prochlorperazine and dimenhydrinate have all been shown to be effective. Combination treatment may be more effective than a single agent especially in moderate-to-high risk patients.
Antiemetic prophylaxis is most effective when given at the end of surgery except for dexamethasone which should be given before induction of anaesthesia.
Metoclopramide in standard doses (10 mg IV) is not effective for prevention of PONV.

Motion sickness
Hyoscine hydrobromide and some of the sedating antihistamines are used. They are more effective if given before motion sickness develops (the first dose is usually given before travel). Hyoscine hydrobromide may be slightly more effective than the sedating antihistamines but may not be as well tolerated.

01.02.01 Antispasmodics
CHLORDIAZEPoxide + CLNIDINiUM BROMiDE

CHLORDIAZEPoxide

Mode of action
Chlordiazepoxide causes depressant effects on the subcortical levels of the CNS and calming effects due to actions on the limbic system and reticular formation.

Indications
Chlordiazepoxide is a benzodiazepine with general properties similar to those of diazepam. It is used in the short-term treatment of anxiety disorders and insomnia. Chlordiazepoxide is also used in muscle spasm, in alcohol withdrawal syndrome, and for premedication.

Contraindications
As for Diazepam

Adverse effect
As for Diazepam

Hepatic impairment: Progressive drowsiness began after 20 days of treatment with chlordiazepoxide in a woman with cirrhosis and hepatitis. One week after stopping the drug the patient could not be roused, and full consciousness was not regained for another week. Accumulation of active metabolites of chlordiazepoxide may have been responsible for the prolonged stupor.

Chlordiazepoxide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Dosage
Chlordiazepoxide is given by mouth as the hydrochloride or the base; the doses given refer equally to both. It may also be administered by deep intramuscular or slow intravenous injection as the hydrochloride. Preparations formulated for intramuscular use are stated to be unsuitable for intravenous administration due to the formation of air bubbles in the solvent. Elderly and debilitated patients should be given one-half or less of the usual adult dose.

The usual dose by mouth for the treatment of anxiety is up to 30 mg daily in divided doses; in severe conditions up to 100 mg daily has been given. For acute or severe anxiety an initial dose of 50 to 100 mg of the hydrochloride has been given by injection, followed if necessary by 25 to 50 mg three or four times daily.

For relief of muscle spasm a dose of 10 to 30 mg daily by mouth in divided doses is recommended, and 10 to 30 mg by mouth may be given before retiring for insomnia associated with anxiety.

For the control of the acute symptoms of alcohol withdrawal chlordiazepoxide or chlordiazepoxide hydrochloride may be given by mouth in a dose of 25 to 100 mg repeated as needed up to a maximum of 300 mg daily. For severe symptoms treatment may be initiated by injection of 50 to 100 mg, repeated if necessary after 2 to 4 hours.

Chlordiazepoxide hydrochloride has also been given for anaesthetic premedication in a dose of 50 to 100 mg intramuscularly one hour before surgery.

CLNIDINiUM BROMiDE

Mode of action
Clidinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine. It inhibits gastric secretion of HCL and Gastro intestinal motility by competitive antagonism of acetylcholine at postganglionic parasympathetic receptor sites in smooth muscle and secretory glands.

Indications
- Adjunct therapy for peptic ulcer.
- Irritable Bowel Syndrome (irritable colon, spastic colon).
- Non-ulcer dyspepsia.

Contraindications
Glaucoma, prostatic hypertrophy, benign bladder neck obstruction, hypersensitivity to clidinium bromide.

Adverse effect
Cardiovascular: Palpitations, bradycardia, tachycardia.
Central nervous system: Drowsiness, flushing, headache, nervousness.
Dermatologic: Urticaria, anaphylaxis, increased body temperature due to decreased sweating.
Gastro intestinal: Altered taste perception, nausea, vomiting, dysphagia, heartburn, constipation, bloated feeling, paralytic ileus, gastroesophageal reflux.
Genitourinary: Urinary hesitancy, retention, impotence, dizziness, insomnia, fever.
Ocular: Blurred vision, mydriasis, photophobia, cycloplegia, increased intraocular pressure.
01.02.02 Antimuscarinics

HYOSCYAMINE (HYOSCINE BUTYL BROMIDE)

Mode of action
Hyoscyamine is a tertiary amine antimuscarinic agent with central and peripheral actions. It is a more powerful suppressant of salivation than atropine and usually slows rather than increases the heart rate, especially in low doses. Its central action differs than that of Atropine in that it depresses the cerebral cortex, especially the motor areas, and produces drowsiness and amnesia.

Indications
Irritable bowel syndrome (IBS).
Renal and biliary colic.
Aid in GI radiology or endoscopy.

Contraindications
There are no contraindications for orally administered Hyoscine, however it should not be administered parenterally in the following conditions:
- Glaucoma.
- Hypertrophy of prostate.
- Mechanical stenosis of the gastrointestinal tract.
- Megacolon.
- Tachycardia.

Drug Interaction
On parenteral administration of Hyoscine Tricyclic antidepressants, Quinidine, and Amantadine can potentiate the anticholinergic effect of Hyoscine.

Adverse Effects
No Atropine-like adverse effects are observed on the salivary glands or sweat secretion when Hyoscine is administered in the usual dose. A slight increase in the pulse rate may occur when it is administered IV, parenteral administration may cause transient disturbances in accommodation.

Specific considerations
Children: Use with caution in children <6 years.

Dosage
IBS, renal and biliary colic
Adult: Oral, 20 mg 4 times daily. IV/IM, 20–40 mg, repeated after 30 minutes if needed. Maximum, 100 mg/day.
Child 6–12 years: Oral, 10 mg 3 times daily. IV/IM, 0.5 mg/kg every 6–8 hours.
Aid in GI radiology: Adult, IV 20 mg as a single dose.

Products
HYOSCYAMINE (HYOSCINE BUTYL BROMIDE) AMPS 20MG/AMPS (BUSCOPAN®, SPASMOPAN®)
HYOSCYAMINE (HYOSCINE BUTYL BROMIDE) ORAL DROPS 0.125 MG/ML 15 ML BOTTLE (NEO-ALLOSPASMIN®)
HYOSCYAMINE (HYOSCINE BUTYL BROMIDE) TABS 10 MG (BUSCOPAN®, DIVIDOL®, SCOPINAL®, SPASMOPAN®, SPASMONORE®)

01.02.03 Dopamine antagonists (Antiemetics)

DOMPERIDONE
Mode of Action:
Enhance gastric emptying and intestinal motility.

Indications
Marketed: Nausea and vomiting, Gastroparesis (idiopathic or diabetic)
Accepted: Stimulation of lactation

Contraindications
Concurrent administration with ketoconazole
Specific considerations
Children: Avoid use unless indicated for cancer chemotherapy. Some practitioners may prefer domperidone to metoclopramide.
Pregnancy: Safe to use; ADEC category B2.
Breastfeeding: Used during first months of breastfeeding to stimulate lactation; mother may be less drowsy than with metoclopramide.

Adverse effects
Common: dry mouth, headache.
Infrequent: hyperprolactinaemia leading to galactorrhoea and gynaecomastia; rash, insomnia.
Rare: extrapyramidal effects.

Dosage
Nausea and vomiting
Adult, 10–20 mg every 6–8 hours; maximum continuous treatment 12 weeks.
Child, 200–400 micrograms/kg every 4–8 hours.
Gastroparesis: 10–20 mg 3–4 times daily for up to 6 months.
Lactation stimulation: 10 mg 3 times daily, taper dose over 7–10 days before stopping.
Maximum: 80 mg daily.

Administration instructions
Give at least half an hour before meals.

Practice points
- does not usually cross the blood–brain barrier significantly so extrapyramidal reactions are rare; may be an alternative to metoclopramide.

Products
DOMPERIDONE SUSP. 5 MG/5ML (AS MALEATE) 100 ML (MOTILAT®, MOTIDON®)
DOMPERIDONE TABS 10 MG (AS MALEATE) (COSTI®, DOMPERIDE®, MOTILAT®, MOTILUM®, PERIDON®)
DOMPERIDONE SUPP 10 MG (MOTILAT®)

METOCLOPRAMIDE

Mode of action
Has central dopamine antagonist activity and may cause extrapyramidal adverse effects (more likely in people <20 years). Metoclopramide enhances gastric emptying and intestinal motility.
Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. It increases the tone and amplitude of gastric contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum, resulting in accelerated gastric emptying and intestinal transit.

Indications
Marketed: Nausea and vomiting, Gastric stasis (e.g. after gastric surgery, diabetic gastroparesis), Aid in GI radiology (increases transit in barium studies), Difficult small intestinal intubation.
Accepted: Gastro-oesophageal reflux disease (GORD), Stimulation of lactation.
Combination with paracetamol: relief of migraine

Contraindications
Phaeochromocytoma.

Specific considerations
Parkinson's disease use with caution as may worsen symptoms; domperidone is preferred.
Depression, avoid long term use as may worsen mental state.
Renal impairment: Reduce dose in moderate and severe impairment.
Elderly: Use lower doses; elderly people are more sensitive to adverse effects.
Children: Avoid use; increased risk of extrapyramidal adverse effects.
Pregnancy: Safe to use; ADEC category A.
Young adults <20 years: use low doses, increased risk of extrapyramidal adverse effects.
Breastfeeding: Used during first months of breastfeeding to stimulate lactation.

Adverse effects
Common: restlessness, drowsiness, dizziness, headache.
Infrequent: extrapyramidal adverse effects, hypertension, hypotension, hyperprolactinaemia leading to galactorrhoea, diarrhoea, constipation, depression.
Rare: agranulocytosis, supraventricular tachycardia, hyperaldosteronism, neuroleptic malignant syndrome, tardive dyskinesia.

**Dosage**

**Nausea and vomiting**

Adult, oral/IV/IM 10 mg every 6–8 hours as needed.

Child, oral/IV/IM 0.15 mg/kg every 6–8 hours as needed.

**Cancer chemotherapy**

Adult, IV 10–40 mg every 4 hours; or IV infusion 1–3 mg/kg over 15 minutes; or SC infusion 40–120 mg over 24 hours.

Child, IV 1–2 mg/kg every 4 hours, maximum daily total of 10 mg/kg.

**GORD, gastric stasis**

Adult, oral 10 mg 4 times daily.

**GI radiology, intubation of intestine**

Adult, IV 10 mg as a single dose.

**Renal impairment**

Moderate impairment, reduce dose by one-quarter.

Severe impairment, halve dose.

**Lactation stimulation**

10 mg 3 times daily, taper dose over 7–10 days before stopping.

**Practice points**

- acute dystonic reactions are best treated by IM/IV benztropine (see 16.2.2 BENZTROPINE)
- choose domperidone for stimulating lactation; drowsiness is common with metoclopramide.

**Products**

METOCLOPRAMIDE AMPS 5 MG/ML (AS HCL)   2 ML AMP (PRIMPERAN®, CLOPRAM®)

**ONDANSETRON**

**Mode of action**

Central and peripheral 5HT3 receptor blockade.

**Indications**

Prevention and treatment of nausea and vomiting; following cancer chemotherapy, postoperative radiotherapy-induced

Nausea and vomiting; associated with cancer chemotherapy postoperative radiotherapy-induced where conventional antiemetics are not tolerated.

**Specific considerations**

Hepatic impairment: Reduce dose in severe impairment.

Children: Seek specialist advice about use in children <2 years.

Pregnancy: Are used; limited data available; ADEC category B1.

Breastfeeding: Contact specialized information service; no data available, although 1 or 2 doses after delivery should not be a concern.

**Adverse effects**

Common: constipation, headache, transient rise in hepatic transaminases

Rare: hypersensitivity reactions (including anaphylaxis), arrhythmias, ECG changes, transient visual disturbances, e.g. blurred vision, (rapid IV administration), extrapyramidal effects, seizures.

**Dosage**

**Cancer chemotherapy**

Adult: Highly emetogenic, first dose, IV 8 mg or oral 24 mg 30 minutes before chemotherapy. Maintenance, oral 4–8 mg every 12 hours for the first 24–48 hours. Moderately emetogenic, first dose, oral/IV 8 mg 1–2 hours before treatment. Maintenance, 4–8 mg every 12 hours for the first 24–48 hours.

Child >2 years: Oral/IV 0.15 mg/kg 30 minutes before treatment and then every 6–12 hours for up to 48 hours.

**Postoperative nausea and vomiting**

Adult: Prevention, IV 4 mg at induction. Treatment, IV 4–8 mg may be given if needed.

Child >2 years: Prevention, IV 0.1 mg/kg up to 4 mg at induction.

Radiotherapy: Adult, oral 8 mg every 8–12 hours for up to 5 days.

Severe hepatic impairment: Do not exceed 8 mg daily.

**Administration instructions**

Give IV injection over at least 5 minutes (or infuse over 15 minutes) as there have been reports of transient adverse
effects if given more rapidly; may be given IM if dose volume is suitable.

**Practice points**
- more effective for acute than delayed symptoms of cancer chemotherapy-induced nausea and vomiting

**Products**
- ONDANSETRON AMPS 4 MG/AMP (AS HCL) 2 ML AMP (ESPASEVIT®, SETRON®, VOMSTAR®, ZOFRAN®)
- ONDANSETRON AMPS 8 MG/AMP (AS HCL) 4 ML AMP (ESPASEVIT®, SETRON®, VOMSTAR®, ZOFRAN®)
- ONDANSETRON TABS 4 MG (AS HCL) (ZEMITRON®, ZOFRAN®)
- ONDANSETRON TABS 8 MG (AS HCL) (SETRON®, ZEMITRON®, ZOFRAN®)

**TROPISETRON**

**Mode of action**
Central and peripheral 5HT3 receptor blockade.

**Indications**
Marketed
- Nausea and vomiting in adults:
  - associated with cancer chemotherapy
  - postoperative
  - radiotherapy-induced
  - where conventional antiemetics are not tolerated

Accepted
- Nausea and vomiting in children:
  - following cancer chemotherapy
  - postoperative

Prevention and treatment of nausea and vomiting: following cancer chemotherapy postoperative
- Nausea and vomiting: associated with cancer chemotherapy postoperative radiotherapy-induced
- where conventional antiemetics are not tolerated

**Specific considerations**
- Pregnancy: Are used; limited data available; ADEC category B3.
- Breastfeeding: Contact specialized information service; no data available, although 1 or 2 doses after delivery should not be a concern.

**Adverse effects**
Common: constipation, headache, transient rise in hepatic transaminases, abdominal pain, diarrhoea, dizziness, fatigue.
Infrequent: hypertension.
Rare: hypersensitivity reactions (including anaphylaxis), arrhythmias, ECG changes, extrapyramidal effects.

**Dosage**
Cancer chemotherapy
- Adult
  - Initially, IV 5 mg 15 minutes before chemotherapy.
  - Maintenance, oral 5 mg daily for 5 days.
- Child >2 years
  - Initially, IV 0.2 mg/kg (up to 5 mg) before chemotherapy.
  - Maintenance, oral/IV 0.2 mg/kg once daily (up to 5 mg) for up to 5 days each cycle.
- Postoperative nausea and vomiting
  - Adult: Prevention and treatment, IV 2 mg daily.
  - Child >2 years: Prevention and treatment, IV/oral, 0.05–0.2 mg/kg (up to 2 mg) once or twice daily.

**Administration instructions**
- Do not give IM. Give IV injection over at least 1 minute or infuse over 15 minutes.

**Counselling**
Take capsules with water at least 1 hour before food.
This medicine may cause dizziness or fatigue in some people. Be careful driving or operating machinery until you know how tropisetron affects you.
Practice points
More effective for acute than delayed symptoms of cancer chemotherapy-induced nausea and vomiting.

Products
TROPISETRON AMPS 5 MG/AMPS (AS HCL) 5 ML AMP (NAVOBAN®)
TROPISETRON CAPS 5 MG (AS HCL) (NAVOBAN®)

01.02.04 Other Antispasmodics

MEBEVERINE
Mode of action
Direct acting smooth muscle relaxant; reduces GI motility and spasm.

Indications
Irritable bowel syndrome, GI disorders associated with smooth muscle spasm

Specific considerations
Pregnancy: No data; ADEC category B2.
Breastfeeding: No data available.

Contraindications
Paralytic ileus.

Adverse effects
dyspepsia, anorexia, constipation, dizziness, insomnia, headache, decreased pulse rate, malaise

Dosage
135 mg 2 times daily.

Products
MEBEVERINE TABS 135 MG (AS HCL) (BEVACOL®, BEVETALIN®, DUSPATALIN®, MEBETALIN®)

01.03 ULCER HEALING DRUGS

01.03.01 H2 Receptor Antagonists

FAMOTIDINE
Mode of action
Competitively block H2 receptors on parietal cells, reducing gastric acid secretion.

Indications
Peptic ulcer disease (PUD), Gastro-oesophageal reflux disease (GORD), Dyspepsia.

Specific considerations
Phenylketonuria: effervescent tablets contain aspartame.
Renal impairment: Although renally cleared, dosage reduction is rarely required in renal impairment.
Surgery: Continue treatment throughout perioperative period.
Pregnancy: Safe to use; ADEC category B1.
Breastfeeding: No adverse effects reported.

Adverse effects
In general these drugs are well tolerated.
Infrequent: hypotension
Rare: headache, tiredness, dizziness, confusion (especially in elderly people), diarrhoea, constipation, rash; thrombocytopenia, agranulocytosis, hepatitis, vasculitis, interstitial nephritis.

Dosage
PUD: Initially, 40 mg once daily in the evening for 4–8 weeks. Maintenance 20 mg once daily in the evening.
GORD: 20 mg twice daily.
Dyspepsia: 20 mg once or twice daily for 4–8 weeks.

Practice points
• in maintenance treatment of PUD and GORD, some specialists use larger doses (up to double those quoted); however there is no evidence of increased benefit and cost advantages over PPIs may be lost
• the efficacy of H₂ antagonists for stress ulcer prophylaxis is controversial; meta-analysis indicates some benefit over placebo in reducing clinically significant bleeding but cost efficacy is questioned; stop prophylaxis when stressors are removed.

**Products**
FAMOTIDINE TABS 40 MG (ACIFAM®, AMODINE®, FAMODAR®, FAMODINE®, GASTRIFAM®, PEPCIDIN®, PEPTIFAM®, STOMAX®, ULCERAN®)

**RANITIDINE**
For additional information see 12.1.3 H₂ antagonists.

**Mode of action**
Competitively block H₂ receptors on parietal cells, reducing gastric acid secretion.

**Indications**
Marketed: Peptic ulcer disease (PUD), Gastro-oesophageal reflux disease (GORD), Dyspepsia
Accepted: Stress ulcer prophylaxis.

**Contraindications**
Acute porphyria.

**Specific considerations**
Phenylketonuria: Effervescent tablets contain aspartame.
Renal impairment: Although renally cleared, dosage reduction is rarely required in renal impairment.
Surgery: Continue treatment throughout perioperative period.
Pregnancy: Safe to use; ADEC category B1.
Breastfeeding: No adverse effects reported.

**Adverse effects**
In general these drugs are well tolerated

**Adverse effects**
Infrequent: Bradycardia (following rapid IV administration), hypotension
Rare: Interstitial nephritis, involuntary movement disorder (reversible), headache, tiredness, dizziness, confusion (especially in elderly people), diarrhoea, constipation, rash (all common with cimetidine); thrombocytopenia, agranulocytosis, hepatitis, vasculitis

**Dosage**
PUD
Oral, initially 300 mg daily as a single evening dose (or 2 divided doses) for 4–8 weeks or IV/IM, 50 mg every 6–8 hours.
Maintenance, oral 150–300 mg daily as a single evening dose.

GORD
Oral, 300 mg daily as a single evening dose, or 2 divided doses.
Stress ulcer prophylaxis:
Oral, 150 mg twice daily until risk factors removed.
IV, 50 mg every 6–8 hours; or 50 mg initially, then IV infusion 125–250 micrograms/kg/hour until risk factors removed.
Dyspepsia: Oral, 150 mg twice daily for 4–8 weeks.
Child: Oral, 2–4 mg/kg twice daily (maximum 300 mg daily). IV, 1 mg/kg (up to 50 mg) every 6–8 hours.

**Administration instructions**
IV, dilute in sodium chloride 0.9% and give over not less than 5 minutes or infuse at 25 mg/hour over 2 hours.

**Products**
RANITIDINE SYRUP 75 MG/5ML (RANIDINE®)
RANITIDINE TABS 300 MG (ANTAGONIN®, HISTAC®, NADINE®, PEPTAC®, RANID®, RANIDINE®, ROLAN®, ZANTAC®)

01.03.03 Chelates and complexes (Cytoprotective agents)

**BISMUTH SUBCITRATE**
See also Helicobacter pylori-related ulcers.

**Mode of action**
Forms an acid- and pepsin-resistant protective coating at the ulcer site. May also have antibacterial effects against H. pylori.

**Indications**
H. pylori eradication (with other agents) after failure of first line treatments.

**Contraindications**
Severe renal impairment.

**Specific considerations**
Pregnancy: Avoid use; bismuth is a heavy metal that crosses the placenta; ADEC category B2. Breastfeeding: Avoid use; excreted in breast milk.

**Adverse effects**
Common: blackening of faeces, darkening of teeth and tongue. Infrequent: nausea, vomiting, dizziness, headache, diarrhea.

**Dosage**
H. pylori eradication: 1 tablet 4 times daily for 10–14 days.

**Administration instructions**
Take on an empty stomach; chew tablets before swallowing. Food or milk may bind with bismuth subcitrate and reduce its efficacy.

**Practice points**
- if a further course is required for ulcer healing, repeat treatment after a 4–8-week interval.

**Products**
BISMUTH SUBCITRATE, COLLOIDAL TABS 120 MG (AS BISMUTH III OXIDE) (DE-NOL®)

01.03.05 Proton Pump inhibitors

**ESOMEPRAZOLE**

**Mode of action**
Irreversibly inactivate the hydrogen/potassium ATPase enzyme system (proton pump), suppressing both stimulated and basal acid secretion. When PPIs are stopped, acid secretion is restored by synthesis of new hydrogen/potassium ATPase.

**Indications**
GORD
H. pylori eradication, as part of an effective regimen
Treatment of gastric ulcer, prevention of peptic ulcer and short term treatment of upper GI symptoms associated with NSAIDs
Dyspepsia
Zollinger–Ellison syndrome
Scleroderma oesophagus
H. pylori eradication, as part of an effective regimen
Prevention and/or treatment of upper GI adverse effects of NSAIDs
In selected patients for stress ulcer prophylaxis, acute upper GI bleeding, prevention of acid aspiration

**Specific considerations**
Gastric carcinoma: exclude before starting treatment for gastric ulcers; PPIs may mask symptoms and delay diagnosis.
Hepatic impairment: Risk of accumulation when higher doses are used; monitor for adverse effects; dosage adjustment not usually required.
Surgery: Continue treatment perioperatively.
Pregnancy: Avoid use, ranitidine preferred; ADEC category B3.
Breastfeeding: Safe to use; all are acid labile; small amount in milk is likely to be destroyed by acid in infant's stomach.

**Adverse effects**
Common: headache, nausea, diarrhoea, abdominal pain, fatigue, dizziness
Infrequent: rash, itch, flatulence, constipation, decreased absorption of cyanocobalamin (vitamin B12) may occur with long term use
Rare: confusion, agitation, aggression, arthralgia, agranulocytosis, PPIs are generally well tolerated.
gynaecomastia, myalgia, interstitial nephritis, raised liver enzymes, hepatitis, jaundice, thrombocytopenia, leucopenia, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, hypersensitivity reactions

**Dosage**
GORD
Initially, oral/IV 20–40 mg once daily; change from IV to oral treatment as soon as possible. Maintenance, reduce to minimum required.

H. pylori eradication
See also Table 01–01 Recommended H. pylori eradication regimens

Oral, 20 mg twice daily for 1 week, with 2 antibiotics.

NSAID-associated upper GI symptoms
Oral, 20 mg once daily for 4 weeks.

Prevention of NSAID-associated peptic ulcer
Oral, 20 mg once daily.

Patient counselling
Swallow tablet whole; do not crush or chew. Alternatively, the tablet may be dispersed in water and taken within 30 minutes. Tell your doctor if you develop symptoms such as black stools or coffee-coloured vomit.

Practice points
- esomeprazole is the S-isomer of omeprazole
- esomeprazole tablets may be dispersed in water and taken within 30 minutes.

Products
ESOMEPRAZOLE AMPS 40 MG (NEXIUM®)
ESOMEPRAZOLE TABS 20 MG (NEXIUM®)

LANSOPRAZOLE

Mode of action
Irreversibly inactivate the hydrogen/potassium ATPase enzyme system (proton pump), suppressing both stimulated and basal acid secretion. When PPIs are stopped, acid secretion is restored by synthesis of new hydrogen/potassium ATPase.

Indications
Marketed: Peptic ulcer disease (PUD), Gastro-oesophageal reflux disease (GORD), H. pylori eradication, as part of effective eradication regimen, Dyspepsia.

Accepted
Zollinger–Ellison syndrome.
Scleroderma oesophagus (seek specialist advice).
In selected patients for stress ulcer prophylaxis, acute upper GI bleeding, prevention of acid aspiration.

Specific considerations
Same as esomeprazole

Adverse effects
PPIs are generally well tolerated.

Common: headache, nausea, diarrhoea, abdominal pain, fatigue, dizziness

Infrequent: pharyngitis, rhinitis, cough, rash, itch, flatulence, constipation.

Rare: agranulocytosis, gynaecomastia, myalgia, interstitial nephritis, raised liver enzymes, hepatitis, jaundice, thrombocytopenia, leucopenia, Stevens–Johnson syndrome, toxic epidermal necrolysis...

Dosage
PUD: Initially, 30 mg once daily for 4–8 weeks. Maintenance, 15–30 mg once daily.

GORD: Adult, initially, 30 mg once or twice daily. Maintenance, reduce to minimum required.

Child >1 year
<30 kg, 15 mg once daily for 8–12 weeks (maximum 30 mg twice daily).
>30 kg, 30 mg once daily for 8–12 weeks (maximum 30 mg twice daily).

Dyspepsia: Initially, 15–30 mg daily for 4–8 weeks.

Zollinger–Ellison syndrome: Adjust dose according to gastric acid output. Initially, 60 mg once daily. Maintenance, 30–180 mg daily (give doses >120 mg daily as 2 divided doses).

H. pylori eradication: 30 mg twice daily for 1 week, with 2 antibiotics.

Severe hepatic impairment: Maximum recommended dose 30 mg daily.

Patient counselling
Swallow capsule whole; do not crush or chew. Alternatively, the capsule may be opened and the contents dispersed in apple, orange or tomato juice, yoghurt or apple sauce; take immediately.

Add the granules to 30 mL of water, stir well and drink immediately.

Tell your doctor if you develop symptoms such as black stools or coffee-coloured vomit.
OMEPRAZOLE

Mode of action
Irreversibly inactivate the hydrogen/potassium ATPase enzyme system (proton pump), suppressing both stimulated and basal acid secretion. When PPIs are stopped, acid secretion is restored by synthesis of new hydrogen/potassium ATPase.

Indications
Marketed: Peptic ulcer disease (PUD), Gastro-oesophageal reflux disease (GORD), Zollinger–Ellison syndrome
H. pylori eradication, as part of effective eradication regimen. Treatment and prevention of peptic ulcer and erosion associated with NSAIDs.
Accepted: Scleroderma oesophagus (seek specialist advice)
In selected patients for stress ulcer prophylaxis, acute upper GI bleeding, prevention of acid aspiration.

Specific considerations
Same as esomeprazole

Adverse effects
PPIs are generally well tolerated.
Common: headache, nausea, diarrhoea, abdominal pain, fatigue, dizziness
Infrequent: decreased absorption of cyanocobalamin (vitamin B12) may occur with long term use rash, itch, flatulence, constipation.
Rare: paraesthesia, confusion, arthralgia, haemolytic anaemia, agranulocytosis, photosensitivity, gynaecomastia, myalgia, interstitial nephritis, raised liver enzymes, hepatitis, jaundice, thrombocytopenia, leucopenia, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis...

Dosage
PUD: Initially, oral 20–40 mg once daily for 4–8 weeks (gastric ulcer). Maintenance, oral 20 mg once daily.
GORD: Initially, oral 20–40 mg once daily (up to 80 mg daily can be used). Maintenance, reduce to minimum required.
Zollinger–Ellison syndrome: Adjust dose according to gastric acid output. Initially, 60 mg once daily. Maintenance, oral 20–120 mg daily (give doses >80 mg daily as 2 divided doses).
H. pylori eradication: Oral, 20 mg twice daily for 1 week, with 2 antibiotics.
NSAID-associated PUD or erosion: Treatment, oral 20–40 mg once daily for 4–8 weeks. Prophylaxis, oral 20 mg once daily.
Child: <10 kg, 5 mg once daily.
10–20 kg, 10 mg once daily (maximum 20 mg/day).
>20 kg, 20 mg once daily (maximum 40 mg/day).

Patient counselling
Swallow tablet or capsule whole; do not crush or chew. Alternatively, omeprazole tablets may be dispersed in water, orange juice or yoghurt; take within 30 minutes.
Tell your doctor if you develop symptoms such as black stools or coffee-coloured vomit.

Practice points
- omeprazole tablets may be dispersed in water, orange juice or yoghurt; give within 30 minutes
- continuous IV administration for 72 hours following endoscopic therapy for bleeding ulcers has been used; seek specialist advice.

Products
OMEPRAZOLE AMPS 40 MG (LOSEC®, OPRAZOLE®)
OMEPRAZOLE TABS OR CAPS 20 MG (HYPOSEC®, LOPRAZ®, LOSEC®, OMEDAR®, OMISEC®, OPRAZOLE®, RISEK®, RYTHMOGASTRY® L OMEPREX®)

PANTOPRAZOLE

Mode of action
Irreversibly inactivate the hydrogen/potassium ATPase enzyme system (proton pump), suppressing both stimulated and basal acid secretion. When PPIs are stopped, acid secretion is restored by synthesis of new hydrogen/potassium ATPase.

Indications
Marketed: Peptic ulcer disease (PUD), Gastro-oesophageal reflux disease (GORD), Zollinger–Ellison syndrome
H. pylori eradication, as part of effective eradication regimen, prevention of dyspepsia, peptic ulcer and erosions associated with NSAIDs in people at increased risk who need continuous nonselective NSAID treatment
Accepted: Scleroderma oesophagus (seek specialist advice)
In selected patients for stress ulcer prophylaxis, acute upper GI bleeding, prevention of acid aspiration.

Specific considerations
Same as esomeprazole

Adverse effects
PPIs are generally well tolerated.
Common: headache, nausea, diarrhoea, abdominal pain, fatigue, dizziness.
Infrequent: dry mouth, increased sweating, rash, itch, flatulence, constipation, decreased absorption of cyanocobalamin (vitamin B12) may occur with long term use
Rare: gynaecomastia, myalgia, interstitial nephritis, raised liver enzymes, hepatitis, jaundice, thrombocytopenia, leucopenia, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, hypersensitivity reactions.

Dosage
PUD: Initially, oral/IV 40 mg once daily for 4–8 weeks; change from IV to oral treatment as soon as possible.
GORD: Initially, oral 40 mg once or twice daily; IV 20–40 mg daily (change to oral treatment as soon as possible).
Maintenance, reduce to minimum required.
Prevention of NSAID-associated dyspepsia, PUD or erosion: Oral, 20 mg once daily.
Zollinger–Ellison syndrome: Adjust dose according to gastric acid output. Usually 80–120 mg oral twice daily or 80 mg 3 times daily.
H. pylori eradication:
Oral, 40 mg twice daily for 1 week, with 2 antibiotics.

Patient counselling
Swallow tablet whole; do not crush or chew.
Tell your doctor if you develop symptoms such as black stools or coffee-coloured vomit.

Products
PANTOPRAZOLE TABS 40 MG (CONTROLOC®, PANTODAR®, PANTOLOC®, PANTOVER®, PROTON®, RAZON®)

01.03.06 OTHER ULCER HEALING DRUGS (GASTROINTESTINAL HAEMORRHAGE)

SOMATOSTATIN
Mode of action
Inhibit release of growth hormone and of various peptides of the gastroenteropancreatic endocrine system.

Indications
Marketed: Acromegaly where surgery or radiotherapy are contraindicated or have failed to control disease, or until radiotherapy becomes fully effective.
Relief of symptoms associated with gastroenteropancreatic tumours, e.g. carcinoid tumours, VIPomas
Prevention of complications following pancreatic surgery (SC octreotide).
Accepted: Glucagonomas (octreotide).

Specific considerations
Insulinoma: possible increase in severity and duration of hypoglycaemia.
Diabetes: variable effect on blood glucose; adjust dose of insulin and oral antidiabetic drugs.
Gastroenteropancreatic endocrine tumours: occasional sudden escape from symptomatic control with rapid recurrence of severe symptoms.
Pregnancy: Avoid use; may produce fetal growth retardation, probably due to suppression of growth hormone;
ADEC category C.
Breastfeeding: Avoid use.

Adverse effects
Common: abdominal pain, flatulence, nausea, vomiting, diarrhoea, gallstones, fatigue, hyperglycaemia, hypoglycaemia, hair loss, transient local reaction at injection site.
Rare: hypothyroidism, pancreatitis, hepatic dysfunction.

Comparative information
There are no direct comparative data between long acting lanreotide and long acting octreotide. They seem to have similar efficacy and safety.

**Practice points**
- monitor thyroid function during long term treatment
- ultrasound of the gall bladder before, and every 6–12 months during, treatment is recommended by the manufacturers.

**Products**
- SOMATOSTATIN (ACETATE HYDRATE) VIALS 0.25 MG/VIAL (SOMATOSTATIN®)
- SOMATOSTATIN (ACETATE HYDRATE) VIALS 3 MG/VIAL (SOMATOSTATIN®)

### 01.04 ACUTE DIARRHOEA

#### 01.04.02 Antimotility Drugs

**LOPERAMIDE**

**Mode of action**
Activate opioid receptors in the gut wall, decreasing bowel motility and increasing fluid absorption.

**Indications**
Diarrhoea, usually short term treatment in adults, Intestinal stoma (to reduce frequency and fluidity of motions).

**Combination with simethicone**
Diarrhoea with associated gas-related abdominal discomfort, short term treatment in adults

**Contraindications**
Intestinal obstruction, Children <2 years.

**Specific considerations**
Pregnancy: 1 or 2 doses safe to use; ADEC category B3, contact specialized information centre.
Breastfeeding: 1 or 2 doses safe to use.
Severe ulcerative colitis: may precipitate toxic megacolon.
Hepatic impairment: Avoid use in severe impairment; may precipitate hepatic encephalopathy.
Children: Avoid use in children <6 years (contraindicated in children <2 years).

**Adverse effects**
Common: abdominal pain and bloating, nausea, vomiting, constipation.
Rare: paralytic ileus, dizziness, rash.

**Dosage**

**Adult**
Acute diarrhoea: Initially, 4 mg, then 2 mg after each loose bowel action.
Intestinal stoma: 4–8 mg daily in 2–3 divided doses. Maximum dose 16 mg daily.
Short gut syndrome diarrhoea: Child, up to 1.25 mg/kg/day in 2–3 doses has been used.
Combination with simethicone
Initially, 2 tablets, then 1 tablet after each loose bowel action. Maximum 4 tablets daily

**Practice points**
- do not use loperamide as an antidiarrhoal in children, especially in those <6 years, except under specialist supervision for diarrhoea associated with short gut syndrome
- use as symptomatic treatment only in adults with acute diarrhoea
- some people with chronic diarrhoea may require long term opioids; this should be a specialist decision.

**Products**
- LOPERAMIDE CAPS/TABS 2 MG (AS HCL) (DIAPEN®, IMODIUM®, IMOTRIL®, LOPERIUM®, RAZENTIL®, VACONTIL®)

### 01.05 CHRONIC BOWEL DISORDERS

#### INFLAMMATORY BOWEL DISEASE

A relapsing and remitting disorder characterised by chronic non-specific inflammation of the GIT. It can also be associated with extra-intestinal symptoms (e.g. fever, skin lesions, eye or joint manifestations). The 2 main forms, Crohn's disease and ulcerative colitis, differ in presentation, site, progression of disease and treatment. Choice of treatment is guided by location, extent, severity and complications of disease as well as response to current or previous treatment.

**Rationale for drug use**
Relieve symptoms.
Induce and maintain remission.
Prevent complications.
Correct and/or prevent nutritional deficiencies.

**Before starting treatment**
Stopping smoking is probably the most important factor in maintaining remission of Crohn's disease. Smoking is associated with a 3–4-fold increased risk of developing Crohn's disease and may also worsen its clinical course. Use NSAIDs with caution in Crohn's disease and ulcerative colitis as they may exacerbate active disease or precipitate a relapse.

**Drug choice**
Includes drugs that control symptoms and those that modify the disease by inducing and maintaining long term bowel healing.

**Symptomatic treatment**

5-Aminosalicylates
Sulfasalazine, mesalazine, olsalazine, balsalazide; used to treat mild-to-moderate inflammatory bowel disease (IBD). There is conflicting evidence regarding their role in maintaining remission in Crohn's disease, but they can be effective maintenance treatment in ulcerative colitis. The 5-aminosalicylates are equally effective; the choice of agent depends mainly on the disease location, dosage forms and adverse effects, e.g. sulfasalazine often causes reversible male infertility.

**Corticosteroids**
Continue corticosteroids only for as long as needed to control acute inflammation, since they are ineffective for maintaining remissions. Patients who require chronic corticosteroid therapy are candidates for immunosuppressants. Topical preparations are effective in left-sided or distal ulcerative colitis. Budesonide is effective in mild-to-moderate ileal or right ileocolonic Crohn's disease; may be better tolerated than other corticosteroids; not used widely due to cost.

**Disease modifying treatment**
Drugs that target the inflammatory processes are usually effective in controlling active disease and may sustain symptomatic remission for prolonged periods.

**Immunosuppressants**
Azathioprine, mercaptopurine, methotrexate and cyclosporin (see Immunosuppressants). Since the onset of action takes 3–6 months, they are not useful for acute disease; use only when prolonged treatment is planned. Consider their use if it has not been possible to wean the patient from corticosteroids after 6 weeks. Crohn's disease: azathioprine and mercaptopurine are effective in treating and maintaining remission in chronically active Crohn's disease which is refractory to, or dependent on, corticosteroids. Methotrexate is also useful for treating this group of patients, and appears promising as maintenance treatment. It is not yet clear how long immunosuppressive agents should be used; benefit of treatment up to 4 years has been shown.
Ulcerative colitis: the role of azathioprine and mercaptopurine in ulcerative colitis is less well defined, but they appear effective in inducing and maintaining remission. There is insufficient evidence for the use of methotrexate in this disease. Cyclosporin can induce remission in severe ulcerative colitis refractory to standard treatment with corticosteroids.

**Infliximab**
Infliximab is generally used in severe Crohn's disease unresponsive to conventional therapy; rapidly induces clinical and endoscopic remission and may provide useful maintenance therapy. Its use is currently limited by uncertainties regarding safety and cost-benefit ratio.

**Other drug treatment**
Metronidazole, alone or with ciprofloxacin, given for up to 3 months may be effective in mild-to-moderate active Crohn's disease. High doses are usually necessary and the adverse effects (especially neurotoxicity) may be limiting. Other antibiotics including clarithromycin, rifabutin and clofazimine, singly or in combination, may be useful. Antidiarrhoeals, such as codeine and loperamide, remain useful in Crohn's disease but are contraindicated in severe ulcerative colitis because of the risk of toxic megacolon. Cholestyramine can reduce diarrhoea due to terminal ileal disease or resection in Crohn's disease. Parenteral vitamin B12 supplements may also be necessary in these patients. Antispasmodics should not be used for IBD. Several other agents have been trialled in IBD although no firm recommendations can be made about their use in routine practice. Thalidomide and immunosuppressants, such as tacrolimus and mycophenolate mofetil, may be of benefit. Nicotine, topical anaesthetic, clonidine, heparin, fish oil and cytokine antibodies, other than infliximab, are...
among a variety of agents being evaluated.

**Non-drug treatment**

Dietary treatment: the role of enteral nutrition in Crohn's disease is controversial. It may induce remission of active disease if taken for 4–6 weeks as the sole nutritional source, but its use is limited by cost, compliance and a high relapse rate when stopped. It is a valuable option in children and is effective in inducing and maintaining remission while promoting linear growth.

There is no evidence that dietary intervention has any specific therapeutic effect in ulcerative colitis.

Probiotics: live bacteria that benefit health by altering the microbial environment. They may be useful in maintaining remission in ulcerative colitis and in the treatment of Crohn's disease.

Other measures: adequate nutrition (including replacing specific deficiencies such as iron, calcium, fat-soluble vitamins) and attention to related secondary complications (such as osteoporosis resulting from malabsorption, corticosteroid therapy or both) are also important. Psychological support is often required.

**Treatment regimens**

**Crohn’s disease**

In active disease oral corticosteroids still provide the quickest and most reliable response; about 70% of patients improve within 4 weeks.

- Acute, mild-to-moderate: limited course of oral corticosteroid or 5-aminosalicylate or antibiotic (e.g. metronidazole, ciprofloxacin).
- Acute, severe: hospital admission; short course of high dose oral or IV corticosteroid. Consider infliximab if response is inadequate.

Maintenance of remission: immunosuppressant (e.g. azathioprine, mercaptopurine, methotrexate). Conventional corticosteroids have no role. Budesonide may prolong time to relapse but does not alter remission rate at 12 months. Despite conflicting evidence regarding their efficacy in sustaining remission, 5-aminosalicylates are commonly used.

Chronic active or refractory disease: immunosuppressant such as azathioprine, mercaptopurine or methotrexate with or without low dose corticosteroid.

**Ulcerative colitis**

- Acute, mild-to-moderate: a 5-aminosalicylate with or without a short course of oral corticosteroid; use rectal preparations for distal disease.
- Acute, severe: hospital admission; short course of high dose oral or IV corticosteroid (usually with 5-aminosalicylate), with or without immunosuppressive agent such as azathioprine. Cyclosporin is used in disease refractory to corticosteroid treatment.

Maintenance of remission: 5-aminosalicylate or immunosuppressant (e.g. azathioprine, mercaptopurine). Corticosteroids are ineffective in maintaining remission.

Chronic active: immunosuppressant (e.g. azathioprine, mercaptopurine) and/or low dose corticosteroid.

**Special cases**

Pregnancy: Seek specialist advice. In pregnant patients it is important to maintain or start treatment to keep inflammatory bowel disease quiescent as uncontrolled disease is a threat to the pregnancy. Give folic acid supplementation.

Breastfeeding: Treatment should be maintained to prevent relapse.

**Practice points**

- infliximab with azathioprine or mercaptopurine may provide long term benefit in Crohn's disease; combination therapy of methotrexate and infliximab is currently under investigation
- using oral and rectal mesalazine is more effective than either alone and is useful in refractory ulcerative colitis.

**01.05.01 Aminosalicylates**

**MESALAZINE**

**Mode of action**

Exact mechanism unknown but exert local anti-inflammatory action in the bowel wall.

**Indications**

Inflammatory large bowel disease, acute and maintenance, Ulcerative colitis, maintenance, rectal Ulcerative colitis, rectal (suppository) and rectosigmoidal (enema) disease.

**Contraindications**: allergy to salicylates

**Specific considerations**
Renal impairment: Use with caution; monitor regularly, especially in severe impairment; possible risk of worsening renal impairment.
Hepatic impairment: Use with caution in severe impairment as hepatically cleared.
Children: not marketed for use in children <12 years but dose below has been used
Surgery: Continue treatment throughout perioperative period.
Pregnancy: Safe to use; ADEC category C.
Breastfeeding: Safe to use.

Adverse effects
More common with higher doses
Common: nausea, rash, headache, diarrhea.
Infrequent: interstitial nephritis.
Rare: neuropathy, blood dyscrasias, pancreatitis (reversible), hepatitis

Dosage
Ulcerative colitis
enema, rectal foam, 2–4 g once daily, enema, suppository, 1 g once daily.
Acute: tablet, 500 mg 3 times daily, tablet, granule, 500 mg – 1 g 3 times daily.
Maintenance: tablet, 250 mg 3 times daily, tablet, granule, 500 mg 3 times daily.

Crohn's disease
Acute: tablet, 500 mg 3 times daily, tablet, 1–1.5 g 3 times daily.
Maintenance: tablet, 250 mg 3 times daily, tablet, 500 mg – 1 g 3 times daily.
Child: tablet, initially, 15–20 mg/kg 3 times daily; maintenance, 10 mg/kg 2–3 times daily.

Counselling
Swallow tablets or granules whole without chewing or crushing them.
Take tablets at least half an hour before food.

Practice points
• the value of mesalazine in small bowel Crohn's disease is controversial

Products
MESALAZINE ENEMA 1 GM (PENTASA®)
MESALAZINE POWDER 1 GM SACHET (PENTASA®)
MESALAZINE SUPP. 1 GM (PENTASA®)
MESALAZINE TABS 500 MG (PENTASA®)

SULFASALAZINE
Mode of action
Exact mechanism unknown but exert local anti-inflammatory action in the bowel wall.

Indications
Ulcerative colitis, acute and remission maintenance, rheumatoid arthritis, Crohn's disease (limited role in colonic disease; much less effective than in ulcerative colitis).

Contraindications
Allergy to sulfonamide or salicylate.

Specific considerations
Blood dyscrasias, increased risk of myelosuppression.
Asthma, severe allergy may be exacerbated.
Renal impairment: Use with caution; monitor regularly, especially in severe impairment; possible risk of worsening renal impairment.
Hepatic impairment: Use with caution in severe impairment as hepatically cleared.
Surgery: Continue treatment throughout perioperative period.
Pregnancy: Safe to use; give a folic acid supplement daily (0.5–5 mg); ADEC category A.
Breastfeeding: Safe to use.

Adverse effects
More common with higher doses.
Common: vomiting, reversible male infertility (oligospermia), haemolysis (not usually severe) nausea, rash, headache, diarrhea.
Infrequent: yellow–orange discolouration of urine or skin interstitial nephritis.
Rare: toxic epidermal necrolysis, fibrosing alveolitis, meningitis, hypersensitivity including serum sickness,
anaphylactoid reactions, arthralgia, itch, blood dyscrasias, pancreatitis (reversible), hepatitis.

**Dosage**

**Ulcerative colitis**
Adult: *Acute*, oral 2–4 g daily in 3–4 doses. Higher doses (up to 8 g daily) are sometimes used but risk of toxicity is increased. *Maintenance*, oral 500 mg 4 times daily.

*Localised rectal*, 1–2 suppositories morning and night after defecation.
Child >2 years: *Acute*, oral 40–60 mg/kg daily in 3–4 doses. *Maintenance*, oral 20–30 mg/kg daily in divided doses.

**Counselling**
Take tablets with food to reduce stomach upset.

**Practice points**
- sulfasalazine's role in Crohn's disease is limited to active disease in patients with colonic involvement
- obtain urinalysis, liver function tests and complete blood examination at baseline and every 2 weeks for the first 3 months of treatment, then at least every 6 months
- soft (hydrogel) lenses may be stained by sulfasalazine use; disposable lenses may still be used
- sulfasalazine impairs absorption of folic acid; consider supplementation, especially before and during pregnancy.

**Products**
**SULFASALAZINE TABS 500 MG** *(PMS-SULFASALAZINE®, SALAZOPYRIN®)*

**01.05.02 Corticosteroids**

**BUDESONIDE**

**Mode of action**
Anti-inflammatory. Formulation delivers budesonide predominantly to the ileum and ascending colon. Systemic absorption is reduced by high first-pass metabolism, producing mainly local effects in the gut. However, some systemic effects occur.

**Indications**
Marketed: Induction of remission in mild-to-moderate Crohn's disease affecting the ileum and/or the ascending colon.
Accepted: Delay relapse during maintenance therapy for Crohn's disease.

**Specific considerations**
Surgery: Continue treatment throughout perioperative period. Depending on the type of surgery additional corticosteroid coverage may be needed to avoid adrenal crisis.
Children: Not recommended.
Pregnancy: Use if indicated; ADEC category B3.
Breastfeeding: Limited data; appears safe.

**Adverse effects**
Infrequent and usually of mild-to-moderate severity. However, adrenal suppression may occur even with short courses of therapy. Despite limited data on prolonged therapy, the possibility of long term glucocorticoid adverse effects should be considered.

**Dosage**
9 mg once daily in the morning just before food.

**Patient counseling**
Swallow the capsules whole, do not crush or chew them.
Do not stop taking this medication suddenly.
Therapeutic effects may take 2–4 weeks to become apparent.
Avoid grapefruit as it may increase the risk of side effects with budesonide.

**Practice points**
- budesonide has a favourable topical activity/systemic effects ratio which may offer benefit over conventional corticosteroids
- high cost limits use
- transfer from a corticosteroid with significant systemic effects to budesonide requires cautious tailoring of dose to avoid adrenal crisis
- wean budesonide slowly as for other corticosteroids.
**Products**
BUDESONIDE ENEMA 2 MG (ENTOCORT®)
BUDESONIDE TABS 3 MG (ENTOCORT®)

**01.06 LAXATIVE DRUGS**

**01.06.01 Bulk Forming Laxatives**

**BULKING AGENTS**
Agents include ispaghula husk, psyllium and sterculia.

**Mode of action**
Absorb water in the colon to increase faecal bulk which stimulates peristaltic activity.

**Indications**
Constipation, Diarrhoea (and occasionally faecal incontinence), to improve stool consistency, Colostomy and ileostomy, to regulate faecal consistency.

**Contraindications**
Intestinal obstruction, partial or complete, Colonic atony.

**Specific considerations**
Renal impairment: Potassium content of products and fluid volume required may be unacceptable in moderate-to-severe impairment.

**Adverse effects**
Common: flatulence, bloating, abdominal discomfort
Rare: allergic reaction (e.g. wheeze, chest tightness, urticaria) with ispaghula, intestinal obstruction, oesophageal obstruction.

**Dosage**
Dose according to product label.

**Practice points**
- use in acute constipation when dietary modification is inadequate
- give with extra fluid to ensure laxative effect, or with minimal fluid to harden stool
- full effect may take several days
- use cost and patient preference to guide choice between agents
- should not be taken immediately before going to bed.
- some products contain frangula (buckthorn) bark which is a stimulant laxative.

**Products**
ISPAGULA HUSK GLUTEN + PLANTAGO OVATA SEEDS + SENNA PODS 100 GM (AGIOLAX®)
STERCULIA+FRANGULA GRANULES COMBINATION 62 % + 8 % 200 GM (NORMACOL PLUS®)

**01.06.02 Stimulant laxatives**

**BISACODYL**

**Mode of action**
Act by direct stimulation of nerve endings in colonic mucosa to increase intestinal motility. May cause accumulation of water and electrolytes in the colonic lumen.

**Indications**
Constipation, Bowel preparation before diagnostic or surgical procedures requiring bowel emptying.

**Contraindications**
Intestinal obstruction, partial or complete, Acute abdominal conditions, e.g. appendicitis, Inflammatory bowel condition.

**Specific considerations**
Elderly: Increased risk of faecal incontinence.
Pregnancy: Avoid direct stimulants except for occasional doses; ADEC category A.
Lactation: May be used.

**Adverse effects**
Infrequent: rectal irritation, proctitis (with rectal administration), abdominal cramps, fluid and electrolyte imbalance (especially hypokalaemia).

**Dosage**
Constipation
Adult: Oral, 5–15 mg as a single dose at night. Rectal, 10 mg once daily when required.
Child: >3 years, oral 5–10 mg as a single dose at night; rectal 5–10 mg once daily as required. <3 years, rectal 5 mg once daily as required.

Bowel preparation: Adult, up to 30 mg orally on the night before the procedure (or 10 mg on each of the 2 nights before the procedure), usually followed by 10 mg rectally on the morning of the procedure.

Practice points
- onset of action is 6–12 hours (oral); 15–60 minutes (suppository); 5–15 minutes (enema)
- may be used long term for constipation in spinal damage, chronic neuromuscular disease and in people taking opioids; often used with other laxatives
- stimulants are the laxative group most often associated with laxative misuse.

Products
- BISACODYL SUPP. 10 MG (DULCOLAX®, LAXADYL®, SACOLUX®)
- BISACODYL TABS 5 MG (BICODYL®, DULCOLAX®, LAXADYL®)

CASTOR OIL
The fatty oil obtained by cold expression from the seeds of Ricinus communis. It is a clear, almost colourless or slightly yellow, viscous, hygroscopic liquid. Miscible with alcohol and with glacial acetic acid; slightly soluble in petroleum spirit.

Indications
Castor oil is used externally for its emollient effect. It has also been used topically to allay irritation due to foreign bodies in the eye. Castor oil may be employed as the solvent in some injections. Castor oil is used for bowel evacuation before radiological procedures, endoscopy, surgery, it has been used as a laxative, but such use is obsolete.

Contraindications
Intestinal obstruction.

Adverse Effects and Precautions
Oral administration of castor oil, particularly in large doses, may produce nausea, vomiting, colic, and severe purgation. Castor oil should be used with caution in pregnancy and menstruation.

The seeds of Ricinus communis contain a toxic protein, ricin. Allergic reactions have been reported in subjects handling the seeds.

Products
- CASTOR OIL, AROMATIC 60-100ML/BOTTLE

GLYCEROL
Also known as glycerin.

Mode of action
Non-absorbable sugar. Osmotic laxative; it draws water into the faeces, has lubricating properties and may also act as a stimulant by its local irritant effects.

Indications
Constipation.

Adverse effects
Infrequent: rectal discomfort.
Rare: rectal mucosal erosion.

Dosage
1 suppository once daily when required.

Practice points
Onset of action is 5–30 minutes

Products
- GLYCERIN SUPP. (ADULT) (JOCERIN®, GLYCERIN®)
- GLYCERIN SUPP. (CHILD) (JOCERIN®, GLYCERIN®)

01.06.03 Osmotic laxatives

LACTULOSE

Mode of action
Poorly absorbed, metabolized by colonic bacteria; it exerts an osmotic effect in the colon. Increase in intraluminal pressure stimulates peristalsis. Beneficial effects in hepatic encephalopathy are thought to result from prevention of absorption of ammonia by lowering faecal pH as well as its laxative effect.

**Indications**  
Constipation, Hepatic encephalopathy.

**Contraindications**  
Intestinal obstruction, partial or complete, Galactose or lactose intolerance (products contain galactose <1.65 g/15 mL and lactose <0.9 g/15 mL).

**Specific considerations**  
Pregnancy: Safe to use.  
Breastfeeding: Safe to use.

**Adverse effects**  
Common: flatulence, abdominal discomfort.  
Infrequent: diarrhoea, electrolyte imbalances.

**Dosage**

**Constipation**  
Adult: Initially 15–30 mL daily in 1 or 2 doses. Doses up to 90 mL daily may be used if necessary. Maintenance, 10–25 mL daily.  
Child: 6–12 years, 15 mL daily. 1–5 years, 5–10 mL daily. <12 months, 3–5 mL daily.  

**Hepatic encephalopathy**  
Adult: Oral/nasogastric tube, 30–45 mL every 1–2 hours to induce rapid laxative effect. Reduce to 30–45 mL 3–4 times daily when laxative effect has been achieved. The dose is subsequently adjusted to produce 2–3 soft stools per day.  
Rectal (if the oral route is unavailable), dilute 300 mL of lactulose oral liquid with 700 mL water or sodium chloride 0.9%; retain enema for 30–60 minutes and repeat every 4–6 hours until the person is able to take orally.  
Child: Oral/nasogastric tube, 1 mL/kg (up to adult dose) every 1–2 hours until desired response, then every 6 hours.

**Counselling**  
This medicine tastes very sweet, it may help to mix it with fruit juice, water or milk.

**Practice points**  
- onset of action is 1–3 days  
- a systematic review concluded there was not enough evidence to determine whether lactulose benefited patients with hepatic encephalopathy

**Products**

**LACTULOSE SYRUP 10 GM/15ML 100-300 ML BOTTLE (LACTUVER®, LAXODAD®, RAMLAC®, RIALAC®)**

**PHOSPHATE ENEMA**

**Mode of action**  
Non-absorbable salts retain fluid in the colon by osmotic effect and stimulate peristalsis.

**Indications**  
Bowel preparation, for GI endoscopic or surgical procedures Chronic constipation.

**Contraindications**  
Intestinal obstruction, partial or complete, Severe colitis, especially toxic megacolon, Phenylketonuria, Heart failure (products containing sodium phosphate), Renal impairment (products containing sodium phosphate; leads to hyperphosphataemia).

**Specific considerations**  
Cardiovascular disease (e.g. heart failure) avoid use of sodium salts; use with caution as fluid and electrolyte disturbances can occur. Electrolyte disturbance may be worsened, avoid use.  
Renal impairment: Avoid use of magnesium or sodium salts; significant fluid and electrolyte disturbance may occur, Elderly: Use with caution; risk of electrolyte disturbance and dehydration.  
Children: Use of sodium phosphate in children <2 years may cause hypocalcaemia.  
Small volume preparations may cause dehydration and electrolyte disturbance if not used with adequate hydration.  
Pregnancy: Other sodium/magnesium laxatives: limited data available; safe to use short term if other agents
ineffective.
Breastfeeding: Safe to use.

Adverse effects
Small volume products that contain sodium phosphate used for bowel preparation can cause serious fluid and electrolyte disturbance, including hypocalcaemia, hyperphosphataemia and hyperkalaemia. Acute renal failure has also been reported.
All sodium or magnesium laxatives may cause nausea, bloating, fluid and electrolyte depletion and rectal irritation. Rectal gangrene has been associated with the use of phosphate enemas in elderly patients and was believed to be due to a direct necrotizing effect of the phosphate on the rectum.

Dosage
See directions on label.

Patient counselling
Bowel preparation, do not eat from 1–2 hours before starting preparation until after procedure performed; clear fluids are permitted; expect diarrhoea usually after about 1 hour and a clear water-like discharge by 4 hours.

Practice points
- onset of action is 30 minutes – 3 hours
- oral medication taken during or within the hour before sodium or magnesium laxative may be flushed from the GIT without absorption
- avoid laxatives containing sodium phosphate in renal impairment
- sodium or magnesium laxatives may be given orally or rectally; they are poorly and slowly absorbed.

Products
PHOSPHATE ENEMA (SODIUM ACID PHOSPHATE+SODIUM PHOSPHATE) 125-133 ML BOTTLE
(PHOSPHATE ENEMA B®, FLETCHERS PHOSPHATE ENEMA®, JO-ENEMA®, KLYSMOL®)

01.07 LOCAL PREPARATIONS FOR ANAL AND RECTAL DISORDERS

PERIANAL DISORDERS
The most common perianal conditions treated with drugs are haemorrhoids, anal fissure and pruritus ani. Many perianal problems require surgical intervention.

Rationale for drug use
Symptom relief.

Before starting treatment
Attention to factors such as diet and hygiene is often an important first step in treating these conditions. Give advice on avoiding prolonged straining. A high fibre diet, adequate fluid intake and bulking agents or stool softeners prevent straining and so may reduce pain associated with haemorrhoids and anal fissure. Consider secondary causes of pruritus ani such as infections (e.g. worms) or skin conditions. To reduce irritation keep area clean and dry, avoid soap products, rough toilet paper and nylon clothing. Simple emollients (e.g. zinc and castor oil cream) applied after cleansing may also help.

Drug choice
Evidence for efficacy of topical anorectal medication is anecdotal. Anorectal products often contain a corticosteroid and/or a local anaesthetic agent. Topical glyceryl trinitrate (0.2%) is available for anal fissures; it provides modest efficacy by relaxing the internal anal sphincter but headache is a common adverse effect.

Practice points
- limit use of topical products to maximum of 7 days as local anaesthetics may cause sensitisation of perianal skin and topical corticosteroids may exacerbate local infection and cause skin atrophy
- topical corticosteroids and local anaesthetics are safe to use in pregnancy and breastfeeding.

01.07.01 Soothing Haemorrhoidal Preparations

ANORECTAL PRODUCTS
Mode of action
Plain anti-haemorrhoidal ointment and suppositories posses' emollient and soothing properties as well as astringent action thus relieving the pain and irritation associated with haemorrhoids.
**Indications**
Haemorrhoids, Anal fissure, Pruritus ani.

**Contraindications**
Hypersensitivity to any of the components, fungal infections, tuberculosis of the skin, vaccinia, varicella, herpes simplex, markedly impaired circulation.

**Adverse effects**
Dermatologic: local burning, itching, irritation, dryness, allergic contact dermatitis, secondary infection, hypopigmentation, folliculitis.

**Dosage**
Use according to manufacturer's product information.

**Products**
- HAEMORRHOIDAL OINTMENT PREPARATIONS, SOOTHING (PROCTOLAIN®)
- HAEMORRHOIDAL SUPP. PREPARATIONS, SOOTHING (PROCTOLAIN®)

01.07.02 Compound Haemorrhoidal Preparations with Corticosteroids

**Indications**
Skin conditions, including internal haemorrhoids, and anal fissures.

**Contraindications**
Hypersensitivity to any of the components, fungal infections, tuberculosis of the skin, vaccinia, varicella, herpes simplex, markedly impaired circulation.

**Adverse effects**
Dermatologic: local burning, itching, irritation, dryness, allergic contact dermatitis, secondary infection, hypopigmentation, folliculitis.

**Products**
- HAEMORRHOIDAL+CORTICOSTEROIDS OINTMENT COMPOUND PREPARATIONS (PROCTOGLYVENOL®, PROCTOHEAL®, PROCTOSYNALAR®, PROCTOLAR CENTER®)
- HAEMORRHOIDAL+CORTICOSTEROIDS SUPP. COMPOUND PREPARATIONS (PROCTOGLYVENOL®, PROCTOHEAL®, PROCTOSYNALAR®, PROCTOLAR CENTER®)

01.07.03 Rectal Sclerosants

**ETHANOLAMINE OLEATE**

**Indications**
Monoethanolamine oleate is used as a sclerosant in the treatment of varicose veins and oesophageal varices. For sclerotherapy of varicose veins, 2 to 5 mL of a 5% solution of monoethanolamine oleate is injected slowly into empty isolated sections of vein, divided between 3 or 4 sites. Injection into full veins is also possible. For sclerotherapy of oesophageal varices, the dose is 1.5 to 5 mL of a 5% solution per varix to a maximum total dose of 20 mL per treatment session. Treatment may be given in the initial management of bleeding varices, then repeated at intervals until the varices are occluded.

**Adverse effect**
Monoethanolamine oleate is irritant to skin and mucous membranes. Local injection may cause sloughing, ulceration, and, in severe cases, necrosis. Pain may occur at the site of injection. Patients receiving treatment for oesophageal varices may develop pleural effusion or infiltration. Hypersensitivity reactions have been reported. Sclerotherapy should not be used to treat varicose veins of the legs in patients with thrombosis or a tendency to thrombosis, or with acute phlebitis, marked arterial, cardiac, or renal disease, local or systemic infections, or uncontrolled metabolic disorders such as diabetes mellitus. Effects on the kidneys: Acute renal failure, which clears spontaneously within 3 weeks, occurred in 2 obese women given sclerosing injections of 15 to 20 mL of a solution containing monoethanolamine oleate 5% and benzyl alcohol 2%.

**Dosage**
By slow injection into empty isolated segment of vein, 2-5 ml divided between 3-4 sites, repeated at weekly intervals.
01.08 DRUGS AFFECTING INTESTINAL SECRETIONS

01.09.01 Drugs affecting biliary composition and flow

URSODEOXYCHOLIC ACID

Mode of action
Unclear; alters bile acid composition resulting in greater concentration of ursodeoxycholic acid; increases bile acid output and bile flow. Some evidence for immunological mechanisms.

Indications
Chronic cholestatic liver diseases (e.g. primary biliary cirrhosis (PBC), primary sclerosing cholangitis, cholestasis related to cystic fibrosis).

Contraindications
Acute cholecystitis/cholangitis or bile duct obstruction.

Specific considerations
Children: Limited data; children with PBC may have an initial deterioration in symptoms which may be alleviated by dose reduction and slow titration of dose.
Pregnancy: Limited data; is used for cholestasis of pregnancy but information on efficacy is lacking; ADEC category B3.
Breastfeeding: Limited data; consult specialist advisory service.

Adverse effects
Generally well tolerated.
Common: diarrhoea
Infrequent: increased itch, increased cholestasis, nausea, vomiting, sleep disturbance.

Dosage
Adult: PBC and chronic cholestatic diseases other than cystic fibrosis, 10–15 mg/kg/day in 2–4 divided doses.
Cystic fibrosis, up to 20 mg/kg/day.
Child: 15–20 mg/kg/day in 2–3 divided doses.

Practice points
- use in PBC improves liver function tests but effect on mortality is unclear; changes in liver function tests are not a clear measurement of efficacy; further studies are required to establish efficacy in PBC
- use in primary sclerosing cholangitis improves liver function tests but does not significantly improve symptoms, histology or survival
- little information available on efficacy in cystic fibrosis.

Products
URSODEOXYCHOLIC ACID TABS 100 MG (URSA®)

01.09.04 PANCREATIC ENZYMES

Mode of action
Pancreatic enzymes are essential for fat, protein and carbohydrate digestion. Supplements aim to correct enzymatic deficiency. All products are of porcine origin.

Indications
Cystic fibrosis, Chronic pancreatitis, After gastrectomy or pancreatic surgery

Contraindications
Hypersensitivity to porcine products

Specific considerations
Pregnancy: Safety not established; seek specialist advice.
Breastfeeding: few data; appears safe

Drug interactions
Decreased effect: calcium carbonate, magnesium hydroxide.
Increased effect: H2 – antagonist (e.g. Famotidine, Cimetidine)
Adverse effects
Common: nausea, vomiting, abdominal pain.
Infrequent: irritation of skin around mouth and anus.
Rare: hyperuricaemia, hyperuricuria, fibrinosing colonopathy (bowel stricture) in children with cystic fibrosis taking high doses.

Dosage:
Dose must be individualised and is guided by stool quality and quantity. Specialist supervision is recommended.
Cystic fibrosis: maximum dose 10 000 units of lipase/kg/day

Counselling
Take this medicine with meals and snacks.
Swallow the capsule whole. Alternatively, open the capsule and sprinkle the granules onto a small amount of soft food (eg apple sauce) and swallow immediately. Do not crush or chew the capsule or granules.
Avoid taking this medicine with hot liquid or food as heat can destroy it.

Practice points
- patients who develop new GI symptoms should be reviewed to exclude fibrosing colonopathy
- the use of pancreatic supplements may not relieve pain of chronic pancreatitis; analgesics may be required.

Products
PANCREATIN (AMYLASE 8,000 IU+LIPASE 10,000 IU+PROTEASE 600 IU) CAPS (MINIMICROSPHERES) (CREON®)

01.08.05 Treatment of hepatic encephalopathy

ORNITHINE ASPARTATE

Mode of action
Ornithine is an aliphatic amino acid. It is used as a dietary supplement.

Indications
It has been used in various indications including the treatment of hyperammonaemia and hepatic encephalopathy.

Products
ORNITHINE ASPARTATE AMPS 5 GM/10ML (HEPA-MERZ®)
Table 01.01 Recommended H. pylori eradication regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage</th>
<th>Duration</th>
<th>Eradication rates</th>
<th>Comments</th>
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<tr>
<td>First line</td>
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<tr>
<td>PPI</td>
<td>standard dose twice daily</td>
<td>7 days</td>
<td>&gt;90%</td>
<td>available as 'single script' therapy via PBS-R;</td>
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<tr>
<td>clarithromycin</td>
<td>500 mg twice daily</td>
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<tr>
<td>amoxycillin</td>
<td>1 g twice daily</td>
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<tr>
<td>First line (consider when amoxycillin unsuitable)</td>
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</tr>
<tr>
<td>PPI</td>
<td>standard dose twice daily</td>
<td>7 days</td>
<td>&gt;80%</td>
<td>metronidazole has relatively high rates of pretreatment resistance and greater likelihood of treatment failure</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>500 mg twice daily</td>
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<tr>
<td>metronidazole</td>
<td>400 mg twice daily</td>
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<tr>
<td>First line (consider when clarithromycin unsuitable)</td>
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<tr>
<td>PPI</td>
<td>standard dose twice daily</td>
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<tr>
<td>amoxycillin</td>
<td>500 mg 3 times daily</td>
<td>14 days</td>
<td>80–90%</td>
<td>metronidazole has relatively high rates of pretreatment resistance and greater likelihood of treatment failure</td>
</tr>
<tr>
<td>metronidazole</td>
<td>400 mg 3 times daily</td>
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<tr>
<td>Second line (failure of first line regimen)</td>
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<tr>
<td>PPI</td>
<td>standard dose twice daily</td>
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<tr>
<td>bismuth subcitrate (SAS)</td>
<td>120 mg 4 times daily</td>
<td>10–14 days</td>
<td>75%</td>
<td>complicated regimen and poorly tolerated</td>
</tr>
<tr>
<td>metronidazole</td>
<td>400 mg 3 times daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>tetracycline</td>
<td>500 mg 4 times daily</td>
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</tr>
</tbody>
</table>

1 most studies quoting eradication rates used omeprazole; other PPIs are equally effective
2 if sensitivity testing unavailable

Table 01.02 Comparison of laxative classes

<table>
<thead>
<tr>
<th>Laxative class</th>
<th>Onset of action</th>
<th>Place in treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>bulking agents</td>
<td>oral, 48–72 hours</td>
<td>acute and chronic constipation</td>
</tr>
<tr>
<td>stool softeners</td>
<td>oral, 24–72 hours; rectal, 5–20 minutes</td>
<td>prevention of straining after rectal surgery and in acute perianal disease; little data to support use in acute or chronic constipation</td>
</tr>
<tr>
<td>stimulant laxatives</td>
<td>oral, 6–12 hours; rectal, 5–60 minutes</td>
<td>short term treatment of moderate-to-severe constipation; regular use in chronic neuromuscular disease, opioid-induced constipation; bowel preparation</td>
</tr>
<tr>
<td>osmotic laxatives</td>
<td>glycerol, lactulose, sorbitol</td>
<td>chronic constipation; second line in acute constipation; opioid-induced constipation</td>
</tr>
<tr>
<td>iso-osmotic, sodium or magnesium salts, including sodium phosphate</td>
<td>oral, 24–72 hours; rectal, 5–30 minutes</td>
<td>chronic constipation; bowel preparation</td>
</tr>
<tr>
<td>iso-osmotic, sodium or magnesium salts, including sodium phosphate</td>
<td>oral, 0.5–3 hours; rectal, 2–30 minutes</td>
<td>chronic constipation; bowel preparation</td>
</tr>
</tbody>
</table>
CHAPTER 02  CARDIOVASCULAR SYSTEM

02.01 POSITIVE INOTROPIC DRUGS

02.01.01 Cardiac glycosides

Cardiac glycosides increase the force of myocardial contraction and reduce conductivity within the atrioventricular (AV) node. Digoxin is the most commonly used cardiac glycoside.

Cardiac glycosides are most useful in the treatment of supraventricular tachycardias, especially for controlling ventricular response in persistent atrial fibrillation.

For management of atrial fibrillation the maintenance dose of the cardiac glycoside can usually be determined by the ventricular rate at rest which should not be allowed to fall below 60 beats /minute except in special circumstances, e.g. with the concomitant administration of a beta-blocker.

DIGOXIN

Mode of action
Increases force of myocardial contraction (positive inotrope) and decreases AV nodal conduction, predominantly by its vagotonic effect on the heart which also results in a negative chronotropic effect. It can increase the excitability of cardiac muscle, particularly at higher doses by inhibition of sodium-potassium ATPase.

Indications
AF or atrial flutter, SVT with AV nodal re-entry, Heart failure

Contraindications
Heart block, second or third degree (without pacemaker),
SVT, bypass tract-mediated (Wolff–Parkinson–White syndrome),
Ventricular tachycardia and fibrillation,
Hypertrophic obstructive cardiomyopathy,
Core pulmonale (acute and chronic),
Constrictive pericarditis.

Specific considerations
Digoxin interacts with many drugs,
Hyperthyroidism, fever: increased sympathetic tone; digoxin relatively ineffective; treat underlying cause and use larger doses or combine with another agent.
Hypothyroidism: may increase sensitivity to digoxin and require smaller doses.
Hypokalaemia, hypomagnesaemia, hypercalcaemia, acidosis, hypoxia: increase risk of digoxin toxicity; correct abnormality if possible.

Acute MI, ischaemic heart disease, mycarditis: increase risk of arrhythmias.
Sick sinus syndrome: risk of severe bradycardia or sinoatrial block; use with caution.
Severe aortic stenosis: digoxin may worsen cardiac function because it increases the force of myocardial contraction.
Renal impairment: Predominantly renally cleared (about 70%); reduce loading dose; in severe impairment and maintenance dose in moderate --to- severe impairment.

Elderly: Reduce dose.
Pregnancy: Safe to use, but dose requirement is not predictable; may require increased dose; used to treat fetal arrhythmias; ADEC category A.
Breastfeeding: Safe to use.

Adverse effects
Digoxin has serious adverse effects including potential to worsen arrhythmia (proarrhythmic effect).
Digoxin has a narrow therapeutic index; adverse effects are related to its plasma concentration and very few occur below 0.8 micrograms/L.
Digoxin usually has an effect on the ECG and may result in prolonged PR interval, ST depression or T wave inversion. Apart from the effect on the PR interval, which is a sign of toxicity, these ECG changes do not necessarily indicate digoxin toxicity or myocardial ischaemia.
In children, arrhythmias (including sinus bradycardia) are the earliest and most frequent indicator that digoxin dosage is too high.

Common: anorexia, nausea, vomiting, diarrhoea, blurred vision, visual disturbances, confusion, drowsiness, dizziness, nightmares, agitation, depression

Infrequent: acute psychosis, delirium, amnesia, shortened QRS complex, atrial or ventricular extrasystoles,
paroxysmal atrial tachycardia with AV block, ventricular tachycardia or fibrillation, heart block, gynaecomastia (long term use)
Rare: xanthopsia (yellow vision), rash, thrombocytopenia, convulsions

**Dosage**
Tailor dose according to renal function, clinical response and therapeutic drug monitoring. These doses are intended as a guide.
Digitalisation with loading dose is necessary only to treat arrhythmias and is not usually required for heart failure.

**Adult:** Loading, oral/IV 250–500 micrograms every 4–6 hours, to a maximum of 1.5 mg.
Maintenance, oral 125–250 micrograms once daily (rarely increased up to 500 micrograms daily).
Child: Loading: Give half of the loading dose initially, then a quarter of the dose at 6–12 hours and the last quarter at 12–18 hours. Infant, child up to 2 years, oral/IV 30–40 micrograms/kg. Child >2 years, oral/IV 30 micrograms/kg.
Maintenance: Oral, 5–10 micrograms/kg daily in 1 or 2 doses; maximum 250 micrograms daily.
Elderly: Loading, oral/IV 125–250 micrograms every 4–6 hours, to a maximum of 500 micrograms.
Renal impairment: Loading, Severe impairment, half usual dose. Maintenance: Adjust dose according to drug concentration monitoring if necessary
Moderate, oral 62.5–125 micrograms once daily.
Severe, oral 62.5 micrograms once daily.
Child
Loading
Give half of the loading dose initially, then a quarter of the dose at 6–12 hours and the last quarter at 12–18 hours.
Infant up to 2 years, oral/IV 30–40 micrograms/kg.
Child >2 years, oral/IV 30 micrograms/kg.
Maintenance
Oral, 5–10 micrograms/kg daily in 1 or 2 doses; maximum 250 micrograms daily.

**Concentration monitoring**
Take blood sample immediately before dose (trough), or at least 6 hours after dose to allow for redistribution. Steady state is reached after about 5 days if renal function is normal (half-life is 36 hours).
The manufacturers recommend a therapeutic range of 0.5–2 micrograms/L (0.5–2 nanograms/mL), although toxic effects can occur within this range, eg:
- Anorexia at approximately 1 micrograms/L
- Nausea at approximately 1.8 micrograms/L
- Vomiting at approximately 3 micrograms/L.
Therefore, clinical benefit must be balanced against the incidence of adverse effects and the dose reduced if appropriate.
Toxicity may occur more commonly in the elderly or in those with electrolyte disturbance, hypoxia or hypothyroidism. Interpret results of concentration monitoring in relation to clinical condition.
Heart failure: Lower concentrations of 0.5–0.8 micrograms/L should be considered for patients with heart failure who are in sinus rhythm, as higher concentrations within the therapeutic range may be associated with increased rates of mortality and hospitalisation.

**Administration instructions**
Give IV over at least 5 minutes; compatible fluids are sodium chloride 0.9%, glucose 5% and glucose/sodium chloride. Do not give IM (unpredictable absorption, local irritation).

**Patient counselling**
Tell your doctor or pharmacist that you are taking digoxin before using any other medicines including over-the-counter and herbal products.

**Practice points**
- Assume that any arrhythmia that occurs in a child taking digoxin is due to the drug until proven otherwise
- Check renal function and electrolyte concentrations before starting digoxin
- Onset of effect occurs 4–6 hours after initial dose
- Stop digoxin if patient reverts to sinus rhythm; it does not have any preventative role in paroxysmal AF or atrial flutter
- If another antiarrhythmic agent is combined with digoxin, try to reduce and then stop digoxin once patient is stable
- regularly assess patients for evidence of digoxin toxicity (including resting heart rate); routine measurement of pulse rate before giving next dose of digoxin is not necessary

**Products**

- DIGOXIN AMPS 0.5MG/AMP 2ML AMP (DIGOXIN®, LANOXIN®)
- DIGOXIN ELIXIR 0.05 MG/ML 60 ML BOTTLE (LANOXIN PG®)
- DIGOXIN TABS 0.0625 MG (LANOXIN®, DIGOXIN®)
- DIGOXIN TABS 0.125 MG (LANOXIN®, DIGOXIN®)
- DIGOXIN TABS 0.25 MG (LANOXIN®, DIGOXIN®)

### 02.02 DIURETICS

Thiazides are used to relieve oedema due to chronic heart failure and, in lower doses, to reduce blood pressure. Loop diuretics are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure. Combination diuretic therapy may be effective in patients with oedema resistant to treatment with one diuretic. Vigorous diuresis, particularly with loop diuretics, may induce acute hypotension; rapid reduction of plasma volume should be avoided.

**Elderly:** Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

**Potassium loss:** Hypokalaemia may occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.

**Hypokalaemia** is dangerous in severe coronary artery disease and in patients also being treated with cardiac glycosides. Often the use of potassium-sparing diuretics avoids the need to take potassium supplements.

In hepatic failure, hypokalaemia caused by diuretics can precipitate encephalopathy, particularly in alcoholic cirrhosis; diuretics may also increase the risk of hypomagnesaemia in alcoholic cirrhosis, leading to arrhythmias. Spironolactone, a potassium-sparing diuretic, is chosen for oedema arising from cirrhosis of the liver.

**Potassium supplements** or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension.

#### 02.02.01 Thiazides and related diuretics

Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption in the proximal segment of the distal convoluted tubule. They act within 1 to 2 hours of oral administration and most have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.

In the management of hypertension a low dose of a thiazide, e.g. bendroflumethiazide (bendrofluazide) 2.5 mg daily, produces a maximal or near-maximal blood pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose, and lipids, with little advantage in blood pressure control.

**Specific considerations**

**Gout:** thiazide-induced rise in serum uric acid concentration may precipitate gout; more likely with higher doses of diuretic.

Heart failure with significant oedema: hyponatraemia may occur, particularly with higher doses in conjunction with a salt restricted diet and/or potassium-sparing diuretics and excess water intake.

Treatment with potassium-lowering drugs, eg amphotericin: increases risk of hypokalaemia; monitor potassium concentration.

Renal impairment: Thiazide diuretics are relatively less effective as diuretics in significant impairment (creatinine clearance <25 mL/minute); however, when used in recommended low doses for hypertension, thiazides lower BP mostly by a vasodilator effect. When used with loop diuretics in heart failure, may reduce renal perfusion and precipitate uremia.

**Hepatic impairment:** In cirrhosis, diuretic-induced volume depletion and/or electrolyte disturbance may precipitate hepatic coma or encephalopathy.

**Elderly:** The elderly are more susceptible to electrolyte imbalance (eg hypokalaemia) and orthostatic hypotension.

**Pregnancy:** Avoid use; may cause electrolyte disturbances or neonatal thrombocytopenia; reduction in maternal blood volume may diminish uteroplacental perfusion; they have no place in treatment of pregnancy-associated hypertension; ADEC category C.
Breastfeeding: Use with caution; theoretically could suppress lactation.

HYDROCHLOROTHIAZIDE

Mode of action
Thiazides are moderately potent diuretics. They inhibit reabsorption of sodium and chloride in the proximal (diluting) segment of the distal convoluted tubule and produce a corresponding increase in potassium excretion. When used in recommended low doses for hypertension, thiazides lower BP mostly by a vasodilator effect.

Indications
Marketed: Hypertension, mild-to-moderate, Oedema associated with heart failure or hepatic cirrhosis
Accepted: treatment of nephrogenic diabetes insipidus, Prophylaxis of renal calculi associated with hypercalciuria

Contraindications
Anuria, Severe renal impairment, Addison's disease, Hepatic precoma and coma

Adverse effects
Effects on glucose tolerance, plasma lipids and male sexual function are minimal with current recommended low doses.
Common: dizziness, weakness, muscle cramps, polyuria, orthostatic hypotension, hyponatraemia, hypokalaemia, hyperuricaemia, hypochloraemic alkalosis, hypomagnesaemia
Infrequent: rash, hyperglycaemia, hypercalcaemia, blurred vision, impotence, dyslipidaemia (increase total cholesterol, LDL and triglyceride concentrations and reduce HDL concentration)
Rare: nausea, vomiting, constipation, diarrhoea, toxic epidermal necrolysis, parotitis, intrahepatic cholestatic jaundice, cholecystitis, pancreatitis, agranulocytosis, aplastic anaemia, haemolytic anaemia, thrombocytopenia, dermatitis, urticaria, photosensitivity, purpura, necrotising vasculitis

Dosage
Hypertension: 12.5–25 mg daily.
Oedema: 25–100 mg daily, or intermittently on 3–5 days each week.
Renal calculi: 50–200 mg daily.

Patient counselling
This medicine is usually taken once daily in the morning. If you are taking it twice a day, take the first dose in the morning and the second dose no later than 6 pm. You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.

Administration instructions
Doses should be taken in the morning.

Practice points
• reserve use of combination products with ACE inhibitors or angiotensin II antagonists for patients stabilised on similar doses of single ingredient products
• combination amiloride and hydrochlorothiazide products have an unnecessarily high content of hydrochlorothiazide (50 mg); no more than 25 mg is usually needed in the treatment of hypertension
• use low doses to reduce the likelihood of metabolic adverse effects; high doses increase this risk without giving additional antihypertensive effect
• may be combined with loop diuretics in patients with severe heart failure to increase diuresis; use small, intermittent thiazide doses with careful monitoring, seek specialist advice
• to manage hypokalaemia due to diuretics, minimise dose of thiazide; if necessary use potassium supplements or potassium-sparing diuretics when potassium is <3.5 mmol/L; potassium-sparing diuretics are simpler to use than potassium salts (potassium replacement requirement is 20–60 mmol daily and one potassium chloride 600 mg tablet contains only 8 mmol potassium)
• hypokalaemia may be difficult to correct in the presence of hypomagnesaemia
• hypokalaemia resulting from the use of diuretics is less likely when they are used with ACE inhibitors or angiotensin II receptor blockers than when used alone

Products
HYDROCHLOROTHIAZIDE TABS 25 MG (ESIDREX®, HYDREX®, MODREX®, MONOZIDE®)

INDAPAMIDE

Mode of action
Thiazides are moderately potent diuretics. They inhibit reabsorption of sodium and chloride in the proximal (diluting) segment of the distal convoluted tubule and produce a corresponding increase in potassium excretion. When used in recommended low doses for hypertension, thiazides lower BP mostly by a vasodilator effect.
**Indications**
Hypertension, mild-to-moderate
Marketed: Hypertension, mild-to-moderate
Oedema associated with heart failure or hepatic cirrhosis
Accepted: Treatment of nephrogenic diabetes insipidus
Prophylaxis of renal calculi associated with hypercalciuria

**Specific Considerations**
Gout: thiazide-induced rise in serum uric acid concentration may precipitate gout; more likely with higher doses of diuretic.
Heart failure with significant oedema: hyponatraemia may occur, particularly with higher doses in conjunction with a salt restricted diet and/or potassium-sparing diuretics and excess water intake.
Treatment with potassium-lowering drugs, eg amphotericin: increases risk of hypokalaemia; monitor potassium concentration.
Renal impairment: Thiazide diuretics are relatively less effective as diuretics in significant impairment (creatinine clearance <25 mL/minute); however, when used in recommended low doses for hypertension, thiazides lower BP mostly by a vasodilator effect.
When used with loop diuretics in heart failure, may reduce renal perfusion and precipitate uraemia.
Hepatic impairment: In cirrhosis, diuretic-induced volume depletion and/or electrolyte disturbance may precipitate hepatic coma or encephalopathy.
Elderly: The elderly are more susceptible to electrolyte imbalance (eg hypokalaemia) and orthostatic hypotension.

**Contraindications**
Anuria, Severe renal impairment, Addison's disease, Hepatic precoma and coma

**Adverse effects**
Effects on glucose tolerance, plasma lipids and male sexual function are minimal with current recommended low doses.
Common: dizziness, weakness, muscle cramps, polyuria, orthostatic hypotension, hyponatraemia, hypokalaemia, hyperuricaemia, hypochloraeic alkalosis, hypomagnesaeimia
Infrequent: rash, hyperglycaemia, hypercalcaemia, blurred vision, impotence, dyslipidaemia (increase total cholesterol, LDL and triglyceride concentrations and reduce HDL concentration)
Rare: nausea, vomiting, constipation, diarrhoea, toxic epidermal necrolysis, paraesthesia, intrahepatic cholestatic jaundice, cholecystitis, pancreatitis, agranulocytosis, aplastic anaemia, haemolytic anaemia, thrombocytopenia, dermatitis, urticaria, photosensitivity, purpura, necrotising vasculitis

**Dosage**
1.25–2.5 mg once daily.

**Administration instructions**
Doses should be taken in the morning.

**Patient counselling**
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.

**Practice points**
- controlled release tablets contain a lower dosage than the standard formulation; risk of hypokalaemia is lower with 1.5 mg controlled release formulation compared with 2.5 mg standard formulation, although still common; they have similar antihypertensive effect
- it is also available with an ACE inhibitor (perindopril); reserve use for patients stabilised on similar doses of single ingredient products
- use low doses to reduce the likelihood of metabolic adverse effects; high doses increase this risk without additional antihypertensive effect
- may be combined with loop diuretics in patients with severe heart failure to increase diuresis; use small, intermittent thiazide doses with careful monitoring, seek specialist advice
- to manage hypokalaemia due to diuretics, minimise dose of thiazide; if necessary use potassium supplements or potassium-sparing diuretics when potassium is <3.5 mmol/L; potassium-sparing diuretics
are simpler to use than potassium salts (potassium replacement requirement is 20–60 mmol daily and one potassium chloride 600 mg tablet contains only 8 mmol potassium)

- hypokalaemia may be difficult to correct in the presence of hypomagnesaemia
- hypokalaemia resulting from the use of diuretics is less likely when they are used with ACE inhibitors or angiotensin II receptor blockers than when used alone

**Products**

**INDAPAMIDE TABS 1.5 MG (NATRILIX SR®)**

**02.02.02 Loop diuretics**

Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces pre-load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure. Diuretic-resistant oedema (except lymphoedema and oedema due to peripheral venous stasis or calcium-channel blockers) can be treated with a loop diuretic combined with a thiazide or related diuretic (e.g. bendroflumethiazide 5–10 mg daily or metolazone 5–20 mg daily).

A loop diuretic is sometimes used to lower blood pressure especially in hypertension resistant to thiazide therapy. Loop diuretics inhibit reabsorption from the ascending limb of the loop of Henlé in the renal tubule and are powerful diuretics. Hypokalaemia may develop, and care is needed to avoid hypotension. If there is an enlarged prostate, urinary retention may occur; this is less likely if small doses and less potent diuretics are used initially.

**Specific considerations**

- **Prostatic obstruction**: use of loop diuretics may precipitate acute urinary retention.
- **Gout**: may be aggravated by diuretic-induced hyperuricaemia, especially in obese patients who consume >6 standard drinks daily.
- **Treatment with ototoxic or nephrotoxic drugs**: increases risk of ototoxicity and nephrotoxicity; use combinations carefully, especially in renal impairment.
- **Treatment with potassium-lowering drugs**, eg amphotericin: increases risk of hypokalaemia; monitor potassium concentration.
- **Renal impairment**: Higher doses are usually required; renal function may worsen; monitor electrolytes and creatinine.
- **Hepatic impairment**: Diuretic-induced electrolyte imbalance may precipitate hepatic encephalopathy.
- **Children**: Frusemide is used most often; there is limited information for ethacrynic acid and bumetanide.
- **Pregnancy**: Avoid use; may cause electrolyte disturbances in the fetus; possible neonatal thrombocytopenia; ADEC category C.
- **Breastfeeding**: Use with caution; theoretically could suppress lactation

**BUMETANIDE**

**Mode of action**

Inhibit reabsorption of sodium and chloride in the ascending limb of the loop of Henle. This site accounts for retention of approximately 20% of filtered sodium; therefore, these are potent diuretics. Produce a rapid and intense diuresis and have a short duration of action (4–6 hours). They are effective over a wide dose range with a dose-related response.

**Indications**

- Oedema associated with heart failure, hepatic cirrhosis, renal impairment and nephrotic syndrome
- Severe hypercalcaemia, in combination with adequate rehydration

**Contraindications**

Previous allergic reaction to bumetanide, Severe sodium and fluid depletion, Anuria.

**Specific considerations**

- **Prostatic obstruction**: use of loop diuretics may precipitate acute urinary retention.
- **Gout**: may be aggravated by diuretic-induced hyperuricaemia, especially in obese patients who consume >6 standard drinks daily.
- **Treatment with ototoxic or nephrotoxic drugs**: increases risk of ototoxicity and nephrotoxicity; use combinations carefully, especially in renal impairment.
- **Treatment with potassium-lowering drugs**, eg amphotericin: increases risk of hypokalaemia; monitor potassium concentration.
- **Renal impairment**: Higher doses are usually required; renal function may worsen; monitor electrolytes and creatinine.
- **Hepatic impairment**: Diuretic-induced electrolyte imbalance may precipitate hepatic encephalopathy.
Elderly: The elderly are more susceptible to electrolyte imbalance (e.g., hypokalaemia) and orthostatic hypotension.

Children: Frusemide is used most often; there is limited information for ethacrynic acid and bumetanide.

Pregnancy: Avoid use; may cause electrolyte disturbances in the fetus; possible neonatal thrombocytopenia; ADEC category C.

Breastfeeding: Use with caution; theoretically could suppress lactation.

**Adverse effects**
Most adverse effects are dose-related.
Common: hyponatraemia, hypokalaemia, hypomagnesaemia, dehydration, hyperuricaemia, gout, dizziness, orthostatic hypotension, syncope

Infrequent: dyslipidaemia, increased creatinine concentration, hypocalcaemia, rash

Rare: myalgia, tinnitus, vertigo, deafness (especially with rapid IV administration), acute pancreatitis, jaundice, thrombocytopenia, haemolytic anaemia, agranulocytosis, interstitial nephritis, exfoliative dermatitis, erythema multiforme, bullous eruptions

**Dosage**
0.5–4 mg once or twice daily, adjusted according to clinical response.

Dose equivalence: 1 mg bumetanide has a diuretic effect equivalent to 40 mg oral frusemide.

**Patient counselling**
This medicine is usually taken once daily in the morning. If you are taking it twice a day, take the first dose in the morning and the second dose no later than 6 pm.

You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.

**Practice points**
- Role of loop diuretics in hypertension is limited to management of excess salt and water retention inadequately controlled by other antihypertensive treatment

**Heart failure**
- Combine with an ACE inhibitor in heart failure
- If hypotension occurs decrease dose of diuretic before that of the ACE inhibitor
- Start with a low dose then adjust according to clinical response; use the lowest effective maintenance dose
- Usually given once daily in the morning although there may be a better clinical response if the drug is given in divided doses rather than as a single dose
- When twice daily dosing is needed to avert orthopnoea the second dose is usually given at midday; diuresis may interfere with sleep if given later than early evening
- Higher doses are necessary in refractory heart failure:
  - A trial of IV frusemide may be more effective than increasing oral doses
  - Increase diuretic effect by adding a thiazide diuretic; use small, intermittent thiazide doses with careful monitoring, seek specialist advice

- Monitor weight and electrolytes
- Hypokalaemia is less likely when diuretics are used with ACE inhibitors or angiotensin II receptor blockers than when used alone

**Products**
BUMETANIDE TABS 1 MG (BURINEX®)

**FRUSEMIDE**

**Mode of action**
Inhibit reabsorption of sodium and chloride in the ascending limb of the loop of Henle. This site accounts for retention of approximately 20% of filtered sodium; therefore, these are potent diuretics.

Produce a rapid and intense diuresis and have a short duration of action (4–6 hours). They are effective over a wide dose range with a dose-related response.

**Indications**
Marketed: Oedema associated with heart failure, hepatic cirrhosis, renal impairment and nephrotic syndrome
Accepted: Severe hypercalcaemia, in combination with adequate rehydration

**Contraindications**
Previous allergic reaction to frusemide, Severe sodium and fluid depletion, Anuria.

**Adverse effects**
Most adverse effects are dose-related.
Common: hyponatraemia, hypokalaemia, hypomagnesaemia, dehydration, hyperuricaemia, gout, dizziness, postural
hypotension, syncope
Infrequent: dyslipidaemia, increased creatinine concentration, hypocalcaemia, rash
Rare: tinnitus, vertigo, deafness (especially with rapid IV administration), acute pancreatitis, jaundice, thrombocytopenia, haemolytic anaemia, agranulocytosis, interstitial nephritis, exfoliative dermatitis, erythema multiforme, bullous eruptions

**Dosage**

**Oedema**

Adult: Oral, initially 20–40 mg once or twice daily, adjusted according to clinical response to maintenance dose of 20–400 mg daily. Maximum dose, 1 g daily. IV/IM, 20–40 mg every 1–2 hours until the desired diuretic effect is obtained; increase dose by 20 mg each time if necessary.

Child: Oral, 1–2 mg/kg every 12–24 hours; up to 6 mg/kg in resistant cases. IV/IM, 0.5–1 mg/kg every 6–12 hours; up to 6 mg/kg in resistant cases.

**Hypercalcaemia:** IV 80–100 mg every 1–2 hours.

**Dose equivalence**

The oral bioavailability of frusemide is about 50% (ie 20 mg IV is equivalent to 40 mg oral).

**Administration instructions**

To avoid ototoxicity IV doses should be given no faster than 4 mg/minute.

Take oral frusemide before food. Effect of food on absorption of frusemide varies with different formulations.

**Practice points**

Same as Bumetanide

**Products**

FUROSEMIDE AMPS 20 MG/AMP 2 ML AMP (DIUSEMIDE®, FUROSEMIDE®, FRUSEMIDE®, LASIX®)

FUROSEMIDE SOLUTION 1 MG/ML 100 ML BOTTLE (DIRAMIDE®)

FUROSEMIDE TABS 40 MG (DIUSEMIDE®, IMPUGAN®, LASIX®, URIMIDE®)

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**02.02.03 Potassium Sparing diuretics**

**SPIRONOLACTONE**

**Mode of action**

Inhibit sodium absorption in the distal tubule by antagonising aldosterone (spironolactone). As a result, they interfere with sodium/potassium exchange and reduce urinary potassium excretion.

Weak diuretics when used alone, but may cause severe hyperkalaemia, especially in the presence of renal impairment or if used with ACE inhibitors, angiotensin II antagonists or potassium supplements.

**Indications**

Marketed: Primary hyperaldosteronism, Refractory oedema associated with secondary hyperaldosteronism, eg cirrhosis of the liver, Hirsutism in females

Accepted: Severe heart failure

**Contraindications**

Hyperkalaemia (potassium >5 mmol/L), Renal failure

**Specific considerations**

Debilitated patients with cardiopulmonary disease or uncontrolled type 1 diabetes: increased risk of hyperkalaemia and of respiratory or metabolic acidosis.

Women with reproductive potential: ensure appropriate contraception is provided.

Treatment with drugs which can increase potassium concentration, eg ACE inhibitors: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.

Renal impairment: Increases risk of hyperkalaemia; avoid use in severe impairment.

Hepatic impairment: In patients with cirrhosis, spironolactone may precipitate the following if metabolic derangements occur: renal failure, hyperchloremic metabolic acidosis (in association with hyperkalaemia), and hepatic encephalopathy. The risk is greater when spironolactone is used with other diuretics.

Elderly: More susceptible to orthostatic hypotension and hyperkalaemia.

Pregnancy: Avoid use; this drug may cause feminisation of the male fetus; ADEC category B3.

Breastfeeding: Appears safe to use.

**Adverse effects**

Common: hyperkalaemia, hyponatraemia, hypochloraemia (especially if combined with thiazide diuretics), weakness, headache, nausea, vomiting, mastalgia

Infrequent: GI cramps, diarrhoea, ataxia, drowsiness, confusion, impotence, gynaecomastia, menstrual irregularities,
mild acidosis, renal impairment
Rare: agranulocytosis, hepatotoxicity, rash, lichen planus, lupus-like syndrome, cutaneous vasculitis, urticaria, alopecia, chloasma, osteomalacia

**Dosage**
Primary hyperaldosteronism, 50–200 mg once daily.
Oedema, Initially 100 mg daily; maintenance 25–200 mg daily.
Hirsutism in females, 50–100 mg once daily.
Severe heart failure, 25 mg once daily; increase to 50 mg daily after 8 weeks if progression of heart failure without hyperkalaemia; decrease to 25 mg every other day if hyperkalaemia occurs.

**Patient counselling**
Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

**Practice points**
- reserve use of spironolactone for hirsutism in females for whom other treatments are not suitable
- in severe heart failure, spironolactone is used with an ACE inhibitor, loop diuretic and, in some cases, digoxin; monitor potassium each week for the first month, then each month for 2 months, then every 3 months and when indicated clinically
- potassium-sparing diuretics are not required routinely in patients on thiazide or loop diuretics; reserve for use if hypokalaemia occurs (serum potassium <3.5 mmol/L)

**Products**
- SPIRONOLACTONE TABS 25 MG (ALDACTONE®, ALDORAM®, NORACTONE®, UNILACTONE®)
- SPIRONOLACTONE TABS 50 MG (ALDORAM®, UNILACTONE®)
- SPIRONOLACTONE TABS 100 MG (ALDACTONE®, ALDORAM®, NORACTONE®, UNILACTONE®)

### 02.02.04 Potassium Sparing diuretics with other diuretics
Amiloride and triamterene on their own are weak diuretics. They cause retention of potassium and are therefore used as a more effective alternative to giving potassium supplements with thiazide or loop diuretics. Potassium supplements must not be given with potassium-sparing diuretics. It is also important to bear in mind that administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can cause severe hyperkalaemia.

Although it is preferable to prescribe thiazides and potassium-sparing diuretics separately, the use of fixed combinations may be justified if compliance is a problem. Potassium-sparing diuretics are not usually necessary in the routine treatment of hypertension, unless hypokalaemia develops.

**AMILORIDE + HYDROCHLOROTHIAZIDE**

**AMILORIDE**

**Mode of action**
Inhibit sodium absorption in the distal tubule either by blocking sodium channels. As a result, they interfere with sodium/potassium exchange and reduce urinary potassium excretion.

Weak diuretics when used alone, but may cause severe hyperkalaemia, especially in the presence of renal impairment or if used with ACE inhibitors, angiotensin II antagonists or potassium supplements.

**Indications**
Marketed: Prevention of diuretic-induced Hypokalaemia, Oedema due to heart failure, hepatic cirrhosis or nephrotic syndrome, as an adjunct to thiazide or loop diuretic
Accepted: Primary hyperaldosteronism
Combination with hydrochlorothiazide
Hypertension, Oedema due to heart failure or hepatic cirrhosis

**Contraindications**
Hyperkalaemia (potassium >5 mmol/L), renal failure

**Specific considerations**
Debilitated patients with cardiopulmonary disease or uncontrolled type 1 diabetes: increases risk of hyperkalaemia and respiratory or metabolic acidosis.

Treatment with drugs which can increase potassium concentration, eg ACE inhibitors: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.
Renal impairment: Increases risk of hyperkalaemia.

Hepatic impairment: In patients with cirrhosis may precipitate renal failure, hyperchloraemic metabolic acidosis (in
association with hyperkalaemia), and hepatic encephalopathy; risk is greater when amiloride is used with other diuretics.
Elderly: More susceptible to orthostatic hypotension and hyperkalaemia.
Pregnancy: Avoid use; treatment during pregnancy may result in electrolyte disturbances in the fetus; ADEC category C.
Breastfeeding: No data available; appears safe to use.

**Adverse effects**
Common: hyperkalaemia, hyponatraemia and hypochloraemia (especially when combined with thiazide diuretics), weakness, headache, nausea, vomiting, constipation, impotence, dizziness, muscle cramps
Infrequent: diarrhoea, anorexia, dry mouth, abdominal pain, flatulence, polyuria, orthostatic hypotension, palpitations (associated with hyperkalaemia), rashes, joint or muscle pain, increased plasma creatinine
Rare: jaundice, eosinophilia, itching, encephalopathy, paraesthesia, increased intraocular pressure

**Dosage**
Prevention of diuretic-induced hypokalaemia, 2.5–5 mg daily.
Oedema, initially 5 mg daily; may need to reduce dose after diuresis achieved.
Primary hyperaldosteronism, 5–20 mg daily.
Combination with hydrochlorothiazide
Hypertension, half a tablet daily.
Oedema, initially 1–2 tablets daily; may be increased up to a maximum of 4 tablets daily; it is usually necessary to reduce dose after initial diuresis achieved.

**Administration instructions**
Doses should be taken in the morning.

**Patient counselling**
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy. Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

**Practice points**
- amiloride is not required routinely in patients taking diuretics
- amiloride is preferred to potassium supplements to prevent diuretic-induced hypokalaemia because of greater convenience and tolerability
- amiloride is available either alone, or in combination with a thiazide diuretic (hydrochlorothiazide 50 mg); the combination product has an unnecessarily high content of hydrochlorothiazide (not more than 25 mg is required to treat hypertension)
- potassium-sparing diuretics are not required routinely in patients on thiazide or loop diuretics; reserve for use if hypokalaemia occurs (serum potassium <3.5 mmol/L)

**Products**
AMILORIDE+HYDROCHLOROTHIAZIDE TABS 5+50 MG (AMURETIC®, APO-AMILZIDE®, MEDOCATEN®, UNIRETIC®)

**TRIAMTERENE + HYDROCHLOROTHIAZIDE**

**TRIAMTERENE**

**Indications**
Oedema, potassium conservation with thiazide and loop diuretics

**Cautions**
May cause blue fluorescence of urine

**Contra-indications**
Hyperkalaemia, hepatic impairment, renal impairment

**Side-effects**
Include gastro-intestinal disturbances, dry mouth, rashes; slight decrease in blood pressure, hyperkalaemia, hyponatraemia; photosensitivity and blood disorders also reported; triamterene found in kidney stones

**Dose**
Initially 150–250 mg daily, reducing to alternate days after 1 week; taken in divided doses after breakfast and lunch; lower initial dose when given with other diuretics

**Patient counselling**
Urine may look slightly blue in some lights
02.03 ANTI-ARRHYTHMIC DRUGS

02.03.01 Drugs for Arrhythmia

ARRHYTHMIAS

Rationale for drug use
- Prevent sudden cardiac death.
- Prevent recurrence of life-threatening arrhythmias.
- Restore haemodynamic stability.
- Restore sinus rhythm.
- Control ventricular rate in AF (without restoring sinus rhythm).
- Provide symptom relief.

Before starting treatment
- Make an accurate diagnosis with a 12-lead ECG together with long rhythm strips from multiple leads.
- Seek, and if possible, treat or remove underlying causes such as heart disease including MI or ischaemia, electrolyte abnormalities, hypoxia, pneumonia, thyroid disease, caffeine or alcohol intake, proarrhythmic drugs.
- Consider the need for antiarrhythmic treatment carefully. Many arrhythmias are benign (e.g., atrial premature contractions, ventricular ectopic beats).

Prolonged QT interval
- The QT interval in the ECG represents ventricular depolarisation and repolarisation. It is normally <440 milliseconds.
- It can be prolonged by factors including genetic abnormalities, electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypocalcaemia), increasing age, female gender, bradycardia, structural heart disease (including heart failure, coronary heart disease) and drugs.
- Prolongation of the QT interval can predispose to a potentially fatal ventricular arrhythmia known as torsades de pointes. The risk is increased with a QT interval of >500 milliseconds or an increase over baseline of >60 milliseconds.
- Drugs can prolong QT interval directly, or indirectly by inhibiting the metabolism and increasing the concentration of other agents known to prolong QT interval. The degree of QT prolongation appears to be related to drug concentration.
- Although not all drugs associated with QT prolongation cause torsades de pointes, avoid their use if possible in patients with congenital long QT syndrome. Otherwise, use them with care, particularly if the patient is already taking a drug which prolongs the QT interval or has another condition associated with QT prolongation.

When to start treatment
- The decision to initiate treatment is influenced by:
  - potential life-threatening nature of arrhythmia symptoms and haemodynamic effects
  - presence of underlying heart disease, especially heart failure, coronary artery disease, valvular heart disease.
- The haemodynamic consequences of most arrhythmias depend on the resulting heart rate and underlying cardiac reserve, rather than their origin. Symptoms such as dizziness, loss of consciousness, hypotension, shortness of breath, heart failure or angina indicate poor tolerance.
- Choose the appropriate management: no treatment, drugs, electrical cardioversion, radiofrequency, surgical ablation or devices (pacemaker, implantable defibrillator).
- Consider immediate cardioversion if symptoms are severe or there is haemodynamic instability.
- Consider prophylactic antiarrhythmic therapy (drugs or devices) in patients who are at high risk of serious arrhythmia and sudden death. Implantable cardiac defibrillators are superior to antiarrhythmic drugs in prolonging survival although high cost limits use.

Drug choice
- Choice of antiarrhythmic drug depends on the arrhythmia, coexisting medical conditions (e.g., heart failure usually precludes the use of drugs with negative inotropic effects other than beta-blockers) and the adverse effects of the drug.
- If arrhythmia is secondary to a specific reversible event (e.g., AF following cardiac surgery or with pneumonia, ventricular arrhythmia after MI or ischaemia), drugs may not be required in the long term.
- Avoid combinations of drugs which may prolong QT interval as the risk of arrhythmias is increased.
- Many antiarrhythmics have the potential to worsen arrhythmias (proarrhythmic effect) and this risk is increased with
use of >1 of these drugs. In addition, combined use, or use with other drugs which have negative inotropic or chronotropic effects, may cause heart failure or significant bradyarrhythmia. Avoid such combinations if possible; some are contraindicated.

**BRADYARRHYTHMIAS**

Sinus bradycardia can be a normal occurrence or result from conditions such as acute MI, sick sinus syndrome, drugs (eg beta-blockers, digoxin, amiodarone), hypothyroidism, hypothermia and raised intracranial pressure. Treat only if symptomatic (uncommon at heart rate >40–45 beats/minute).

Sick sinus syndrome includes wide variety of abnormalities of sinus node function such as persistent sinus bradycardia, sinoatrial block, sinus arrest, tachycardia-bradycardia syndrome and junctional or ventricular escape rhythms. It is usually due to idiopathic fibrosis of the node, but is also associated with myocardial ischaemia and digoxin toxicity.

Atrioventricular block causes include myocardial ischaemia, infection and drugs (eg beta-blockers, digoxin, diltiazem, verapamil). Management depends on the type of block and the presence of symptoms.

**Drug choice**

Atropine or isoprenaline may be used to treat bradyarrhythmias resulting in haemodynamic compromise. Atropine is short acting; isoprenaline is given by prolonged infusion for a longer duration of action. Pacemaker insertion is the preferred treatment for persistent bradycardia.

**TACHYARRHYTHMIAS**

Atrial tachyarrhythmias: sinus tachycardia, AF and atrial flutter.

SVT: atrial tachycardia and arrhythmias arising from the atrioventricular (AV) junction (junctional tachycardias).

Ventricular tachyarrhythmias: premature ventricular ectopics, ventricular tachycardias (non-sustained, sustained, torsades de pointes) and ventricular fibrillation.

**Sinus tachycardia**

Usually a physiological response to precipitants such as pain, hypovolaemia, pyrexia, anxiety, but may be due to sympathomimetic drugs or thyrotoxicosis. If there is no obvious cause, drug treatment is not necessary unless symptoms are troublesome, in which case beta-blockers or controlled release verapamil can be used.

**ATRIAL FIBRILLATION**

The most common sustained arrhythmia and is associated with a high incidence of stroke and heart failure. It may be:

- paroxysmal (intermittent and recurrent but terminates spontaneously)
- persistent (cardioversion required to return to sinus rhythm)
- permanent (cannot be terminated by cardioversion).

The aim of treatment is either to restore and maintain sinus rhythm (rhythm control) or to control the rate while allowing the arrhythmia to continue (rate control).

Consider antithrombotic treatment in all patients except those at low risk of stroke..

Paroxysmal AF: use antiarrhythmic drugs if necessary for troublesome symptoms; rate control alone may be appropriate for brief or minimally symptomatic recurrences.

Persistent and permanent AF: control of ventricular rate is now the initial strategy for most of these patients. It is at least as effective as rhythm control in reducing overall mortality and risk of stroke and there are fewer adverse drug effects.

**Control ventricular rate (acute or chronic)**

Aim for a ventricular rate <90 beats/minute at rest and <180 beats/minute on exercise. Some patients have a controlled ventricular rate (because of associated AV nodal disease) and do not require specific treatment.

Use beta-blocker, verapamil, diltiazem or digoxin.

Digoxin alone is relatively ineffective in slowing rapid ventricular rate associated with increased sympathetic tone (eg exercise, hyperthyroidism, fever, hypoxia).

If monotherapy is ineffective, consider combining digoxin with beta-blocker, verapamil or diltiazem.

Do not combine verapamil with beta blockers; risk of bradycardia and reduced cardiac output.

Short term control of ventricular rate in preparation for electrical cardioversion is usually done with a beta-blocker or verapamil (rather than digoxin) to avoid post-conversion digoxin arrhythmias.

In some cases other drugs, such as amiodarone, may be appropriate; seek specialist advice.

**Restore and maintain sinus rhythm**

Cardioversion (electrical or drug-induced) is still appropriate for many patients; seek specialist advice.

Flecainide, disopyramide, quinidine, sotalol and amiodarone can be used. Amiodarone is considered to be the safest agent in heart failure.

Digoxin does not restore sinus rhythm.

**Prevent thromboembolic complications**
Assess the risk of stroke for each patient and reassess regularly. The risk appears to be the same for paroxysmal, persistent or permanent AF.

Recent trials indicate that patients with AF managed by rhythm control continue to be at risk of thromboembolism even when sinus rhythm is achieved and maintained; consider long term or lifelong antithrombotic therapy in all patients.

Warfarin reduces the risk of stroke by about 60%, while the reduction with aspirin is about 20%. The choice of antithrombotic depends on balancing the risk of thromboembolism against the risk of drug-associated haemorrhagic complications.

Low risk: age <65 with no history of embolism, hypertension, diabetes or other clinical risk factors; no antithrombotic treatment.

Moderate risk: age <65 with diabetes or hypertension and all patients aged >65 not in the high risk group; choose between warfarin (INR 2–3) and aspirin (75–300 mg daily).

High risk: previous TIA or stroke, valvular heart disease, age >65 with diabetes and hypertension, heart failure, thyroid disease, impaired left ventricular function on echocardiography; give warfarin (INR 2–3).

If warfarin is contraindicated, use aspirin.

Other approaches to stroke prevention in AF are being explored such as combination antiplatelet therapy (dipyridamole or clopidogrel with aspirin) and use of direct thrombin inhibitors.

**Atrial flutter**

The causes, haemodynamic consequences and management of atrial flutter are similar to those of AF. However, do not use flecainide alone because one-to-one AV conduction may occur; add digoxin or verapamil or beta-blocker.

**Paroxysmal Supraventricular tachycardias**

In most patients this remits spontaneously or can be returned to sinus rhythm by reflex vagal stimulation with respiratory manoeuvres, prompt squatting, or pressure over one carotid sinus (important: pressure over carotid sinus should be restricted to monitored patients: it can be dangerous in recent ischaemia, digitalis toxicity, or the elderly). If vagal stimulation fails, intravenous administration of adenosine is usually the treatment of choice. Intravenous administration of verapamil is useful for patients without myocardial or valvular disease (important: never in patients recently treated with beta-blockers, see VERAPAMIL). For arrhythmias that are poorly tolerated, synchronised d.c. shock usually provides rapid relief.

In cases of paroxysmal supraventricular tachycardia with block, digitalis toxicity should be suspected. In addition to stopping administration of the cardiac glycoside and giving potassium supplements, intravenous administration of a beta-blocker may be useful. Specific digoxin antibody is available if the toxicity is considered life-threatening.

**Atrial tachycardia**

Arises from an ectopic source in the atrial muscle. It can be benign and brief, particularly in elderly people, or can be multifocal or associated with AV block. Multifocal atrial tachycardia usually occurs when the atria are enlarged (chronic pulmonary disease, hypoxia, electrolyte and acid-base disturbances, chronic heart failure). Atrial tachycardia with AV block is typically seen with digoxin toxicity.

In general, treatment is aimed at the underlying cause. Multifocal atrial tachycardia may be mistaken for AF, but does not respond well to digoxin. Adenosine, verapamil or a beta-blocker may be effective if tolerated; otherwise, seek specialist advice.

**SVT with AV nodal re-entry**

Involves re-entry circuits contained within the AV node.

Acute treatment: usually remits spontaneously or with vagotonic manoeuvres (Valsalva manoeuvre, swallowing ice-cold water) which are more effective if used early.

Avoid carotid sinus massage in elderly (risk of atrial emboli from a stenosed carotid artery)

If the arrhythmia persists, use verapamil or adenosine. In some cases cardioversion or other drugs may be appropriate, seek specialist advise.

Avoid verapamil for broad complex tachycardia of unknown origin (SVT with aberrant conduction, Wolff–Parkinson-White syndrome, ventricular tachycardia); treat as ventricular tachycardia.

Preventive treatment: consider if the symptoms are disabling or if the risks associated with recurrence of arrhythmia outweigh the risks of treatment. Verapamil or beta-blockers reduce the severity of symptoms, while flecainide, sotalol or amiodarone reduce episode frequency. Adding a beta-blocker may improve efficacy of antiarrhythmic agents. Radiofrequency ablation is another option.

Do not combine verapamil with beta blockers; risk of bradycardia and reduced cardiac output.

**SVT, bypass tract-mediated (AV re-entry)**

Associated with an accessory conduction pathway outside the AV node (the most common example is Wolff–Parkinson–White syndrome).

Regular tachycardia, treat as SVT with AV nodal re-entry.
Irregular tachycardia, (ie AF in patient with Wolff–Parkinson–White syndrome), use flecainide, sotalol or amiodarone.

Avoid using AV nodal blockers (verapamil, digoxin, beta-blocker, adenosine) in patients with Wolff–Parkinson–White syndrome and AF (risk of ventricular fibrillation).

**Radiofrequency ablation**
May be used to prevent recurrence of both types of SVT. This avoids long term exposure to antiarrhythmic treatment.

**Premature ventricular ectopics**
Ectopics associated with anxiety, stress, caffeine or alcohol may lessen with reassurance and avoidance. If symptoms are troublesome, consider using beta-blockers.

**VENTRICULAR TACHYCARDIA**

**Non-sustained ventricular tachycardia:** drug treatment is usually required only if associated with symptoms or haemodynamic compromise. Use lignocaine initially, and if ineffective, give sotalol or amiodarone.

Sustained ventricular tachycardia: may lead to cardiac arrest. Consider DC cardioversion early if there is haemodynamic collapse or if acute drug treatment is unsuccessful.

**Prevention:** long term prophylaxis may not be required if onset of ventricular tachycardia is within 24 hours of MI or is clearly due to another reversible cause. Treatment options, either alone or in combination, include drugs (sotalol, amiodarone, beta-blockers), implantable cardiac defibrillator and radiofrequency or surgical ablation; seek specialist advice.

**Torsades de pointes**
Associated with conditions that prolong the QT interval. It is usually self-limiting, but can recur if the underlying cause is not corrected. Occasionally it may be prolonged or deteriorate into ventricular fibrillation with sudden death.

Emergency treatment with drugs (eg isoprenaline, magnesium), cardiac pacing or electrical cardioversion can be used until the cause is corrected.

Prevention includes beta-blockers, surgical sympathectomy and implantable cardiac defibrillator as well as avoiding known precipitants.

**ADENOSINE**

**Mode of action**
Depresses sinus node activity and slows conduction through the atrioventricular node; also produces peripheral and coronary vasodilation. Adenosine has a rapid onset and short duration of action.

**Indications**
Acute treatment of SVT, Diagnostic aid for broad or narrow complex tachycardia. For use with radionuclide myocardial perfusion imaging in patients unable to exercise adequately

**Contraindications**
Heart block, second or third degree (without pacemaker), Sick sinus syndrome (without pacemaker), Asthma

**Specific considerations**
AF, atrial flutter: may rarely accelerate ventricular rate.
Obstructive lung disease: may precipitate severe bronchospasm.
Heart transplant: increased sensitivity; reduce initial dose.
Pregnancy: Extremely short duration of action and short half-life make it the treatment of choice when indicated; ADEC category B2.
Breastfeeding: safe to use

**Warnings and precautions:**Patients with pre-existing S-A nodal dysfunction may experience prolonged sinus pauses after adenosine. There have been reports of atrial fibrillation/flutter in patients with PSVT associated with accessory conduction pathways after adenosine. Adenosine decreases conduction through the AV node and may produce a short-lasting first, second, or third degree heart block. Because of the very short half-life, the effects are generally self-limiting. Rare prolonged episodes of asystole have been reported, with fatal outcomes in some cases. At the time of conversion to normal sinus rhythm, a variety of the new rhythms may appear on the ECG. A limited number of patients with asthma have received adenosine and have not experienced exacerbation of their asthma. Adenosine may cause bronchoconstriction in patients with asthma and should be used cautiously in patients with obstructive lung disease not associated with bronchoconstriction (eg, emphysema, bronchitis). Breastfeeding: safe for use

**Adverse effects**
Adverse effects resolve rapidly on stopping treatment due to its short duration of action.
Common: flushing, dyspnoea, chest pain, nausea, headache, dizziness
Infrequent: transient arrhythmias, recurrence of SVT, hypotension

**Dosage**
SVT, diagnostic aid for tachycardia
Adult, initially 3 mg by rapid IV bolus; if unsuccessful within 1–2 minutes, give 6 mg as a second dose; if still unsuccessful within 1–2 minutes, give 12 mg as a third dose.
Child, initially 0.05 mg/kg by rapid IV bolus, increase by 0.05 mg/kg/dose every 2 minutes to a maximum of 0.25 mg/kg/dose (dose not to exceed 12 mg).
Radionuclide perfusion imaging, Continuous IV infusion, 140 micrograms/kg/minute over 6 minutes; seek specialist advice.

Products
ADENOSINE VIALS 6 MG/VIAL  2 ML VIAL (ADENOSINE®, ADENOCOR®)

AMIODARONE
Mode of action
Decreases sinus node and junctional automaticity, slows AV and bypass tract conduction and prolongs refractory period of myocardial tissues (atria, ventricles, AV node and bypass tract); also has weak beta-blocker activity and is a structural analogue of thyroid hormone.

Indications
Treatment and prophylaxis of serious arrhythmias refractory to other treatment, including ventricular arrhythmias, atrial tachyarrhythmias and SVT (AV nodal re-entry or bypass tract-mediated)

Contraindications
Heart block, second or third degree (without pacemaker), Symptomatic bradycardia (without pacemaker), Sick sinus syndrome (without pacemaker), Allergy to amiodarone or iodine

Specific considerations
Thyroid dysfunction, including goitre or nodules: increased risk of hypo- or hyper-thyroidism.
Lung disease (particularly with reduced diffusion capacity): less reserve to cope with pulmonary adverse effects should they occur.
Heart failure: amiodarone is the least negatively inotropic antiarrhythmic and is usually well tolerated in heart failure.
Electrolyte disturbances (eg hypomagnesaemia, hypokalaemia, hyperkalaemia): increased risk of arrhythmias; correct before starting treatment if possible.
Risk factors for prolonged QT interval: Amiodarone may further prolong the QT interval and increase risk of arrhythmia; correct underlying cause if possible; otherwise avoid.
Amiodarone may interact with other medications for weeks to months after it is stopped (very long half-life).
Hepatic impairment: Reduced metabolism and risk of accumulation and/or hepatotoxicity; use with caution.
Elderly: GI adverse effects are more frequent in the elderly, are usually dose-related and improve with time.
Children: Injection contraindicated in neonates as presence of benzyl alcohol can cause fatal 'gasting syndrome'.
Pregnancy: Avoid use 3 months before and during pregnancy; may cause thyroid dysfunction and bradycardia in the fetus; check thyroid function in newborns exposed to amiodarone in utero; ADEC category C.
Breastfeeding: Do not use; excreted in breast milk.

Adverse effects
Amiodarone has serious adverse effects including potential to worsen arrhythmia (proarrhythmic effect); they are slow to resolve after it is stopped (very long half-life).
Many of the adverse effects are related to dose and duration of treatment and may not appear for weeks, months or even years after starting amiodarone.
Common: nausea and vomiting (especially while loading), constipation, anorexia, taste disturbance (metallic taste, loss of taste), transient elevation of hepatic transaminases, hyper- or hypo-thyroidism, fever, photosensitivity, skin pigmentation (blue-grey), benign cornal microdeposits, headache, dizziness, fatigue, neurotoxicity (tremor, ataxia, paraesthesia, peripheral neuropathy, limb weakness), sleep disturbances (vivid dreams or nightmares), pulmonary toxicity, bradycardia, hypotension (IV infusion)
Infrequent: atrioventricular block (IV infusion), arrhythmias (new or exacerbated), phlebitis (peripheral vein), epididymitis
Rare: hepatitis, optic neuropathy, bronchospasm, acute respiratory distress syndrome, heart failure, torsades de pointes, thrombocytopenia, decreased libido, alopecia, allergic skin rash
Pulmonary toxicity: Two main types: an acute inflammatory disorder which can develop early or late, is reversible if drug withdrawn early and which may respond to corticosteroids; and a chronic fibrotic form which is associated with prolonged amiodarone exposure and is less reversible.

Dosage
Adult
Acute treatment of atrial, supraventricular or ventricular tachyarrhythmias
Emergency, IV 150–300 mg over 1–2 minutes (monitor clinical signs and ECG very closely). Loading, IV infusion 5 mg/kg over 20 minutes to 2 hours. Maintenance, IV infusion 15–20 mg/kg over 24 hours; begin oral treatment as soon as possible after IV treatment; overlap oral and IV treatment by 2 days.

Chronic treatment of atrial, supraventricular or ventricular tachyarrhythmias
Oral, 200–400 mg 3 times daily for 1 week, followed by 200–400 mg twice daily for 1 week.
Maintenance, 100–400 mg once daily.
Child: Round doses to nearest quarter tablet (25 mg) if possible. 4 mg/kg 3 times daily for one week, then twice daily for 1 week. Maintenance, 4 mg/kg once daily.
The following IV doses have been used based on limited data:
Child > 1 month, IV, 25 micrograms/kg/minute for 4 hours, then 5–15 micrograms/kg/minute (maximum 1200 mg/24 hours).

Concentration monitoring
Therapeutic range, 1–2.5 mg/L.
Concentration monitoring is rarely necessary in practice. Adverse effects may occur within the therapeutic range. The maximum effect of dosage change is not seen for 1–3 months or more because half-life is 27–107 days.

Administration instructions
Use non-PVC giving sets, glucose 5% injection; infuse via large or central vein; incompatible with sodium chloride 0.9%.

Patient counselling
While taking amiodarone avoid sun exposure, wear protective clothing whenever outdoors, use sunscreen (broad spectrum, factor 30+ sunscreen containing titanium dioxide is recommended).
Amiodarone interacts with grapefruit juice and many other drugs; avoid grapefruit and tell your doctor or pharmacist that you are taking amiodarone before starting any new medication.
You will need regular blood tests, ECGs and chest x-rays while taking amiodarone.
Tell your doctor if you develop shortness of breath or a dry cough, problems with your vision, weight loss, muscle weakness or worsening of your heart symptoms.
Regular blood tests are required.

Practice points
• in general, use lowest maintenance dose necessary to control arrhythmia

Monitoring
• during IV administration monitor BP; severe hypotension and circulatory collapse can occur with rapid infusion
• before starting amiodarone, check baseline clinical status, serum potassium, thyroid and liver function, lung function (including chest x-ray), and ECG; repeat 6 monthly during treatment
• check ECG for significant QT prolongation (>500 milliseconds)
• amiodarone contains 75 mg iodine in each 200 mg tablet and affects thyroxine metabolism; it complicates the diagnosis of thyroid dysfunction; when requesting thyroid function tests, notify laboratory that the patient is taking amiodarone; seek specialist advice
• thyroid function abnormalities and the risk of developing hyper- or hypothyroidism persist for at least 3 months after stopping treatment; liver damage may develop up to a year after stopping treatment
• if dyspnoea or nonproductive cough develop, perform chest x-ray and pulmonary function tests as soon as possible and monitor closely
• perform eye examination annually; essential for those who develop visual symptoms

Products
AMIODARONE AMPS 150 MG/AMP (AS HCL)  3 ML AMP (CORDARONE®, SEDACORON®)
AMIODARONE TABS 200 MG (AS HCL) (ADVADARONE®, CORDARONE®, SEDACORON®)

FLECAINIDE
Mode of action
Slows cardiac conduction and to a lesser extent, increases refractory period in all myocardial tissues (including bypass tracts) but particularly in the His–Purkinje (ventricular conduction) system. Also has negative inotropic activity.

Indications
SVT, Paroxysmal AF or atrial flutter associated with haemodynamic impairment, Serious ventricular arrhythmias refractory to other treatment (including DC shock)
Do not use flecainide to suppress ventricular ectopic activity in patients with coronary artery disease as clinical trials have demonstrated an increased mortality in such patients.

**Contraindications**
Heart block, second or third degree or bifascicular (without pacemaker), Cardiogenic shock, History of MI, Concurrent treatment with quinidine, disopyramide, procainamide

**Specific considerations**
Structural heart disease (particularly with impaired left ventricular function), chronic AF: Flecanide increases risk of ventricular arrhythmias; use with extreme caution and only if refractory to other antiarrhythmics.
Sick sinus syndrome: increases risk of significant bradyarrhythmia; use with extreme caution and only if pacing facilities available.
Permanent or temporary pacing: pacing threshold may be increased; risk of rhythm disturbances; use with caution and monitor regularly.
Heart failure: may be exacerbated because of negative inotropic effect.
Electrolyte disturbances (eg hypomagnesaemia, hypokalaemia, hyperkalaemia): increased risk of arrhythmias; correct before starting treatment if possible.
Renal impairment: Reduce dose according to plasma concentration.
Hepatic impairment: Reduce dose according to plasma concentration.
Pregnancy: Flecainide has been used to treat fetal arrhythmias; seek specialist advice; ADEC category B3.
Breastfeeding: Minimal excretion in breast milk; considered to be safe, but monitor infant.

**Adverse effects**
Flecainide has serious adverse effects including the potential to worsen arrhythmia (proarrhythmic effect).
Common: nausea, vomiting, diarrhoea, constipation, headache, dizziness, tinnitus, visual disturbances, fatigue, tremor, nervousness, paraesthesia, ataxia, heart block (first degree), angina, arrhythmias (new or exacerbated), worsening heart failure, dyspnoea, flushing, increased sweating, rash
Infrequent: bradyarrhythmias, hallucinations, amnesia, confusion
Rare: heart block (second or third degree), cardiac arrest, sudden death, myalgia, arthralgia, fever, decreased libido, urinary symptoms, hepatic dysfunction, pneumonitis (with long term use)

**Dosage**
**Adult**
IV, 2 mg/kg/dose over at least 10 minutes to a maximum of 150 mg.
Oral, 50–100 mg twice daily; increase by 50 mg every 4 days up to a maximum of 400 mg daily.

**Child**
IV, 0.5 mg/kg/dose over at least 10 minutes to a maximum of 2 mg/kg.
Oral, initially 2 mg/kg twice daily; increase dose at intervals >4 days to maximum 6 mg/kg daily in 1–2 doses.

**Concentration monitoring:** Therapeutic range 0.2–0.9 mg/L.

**Administration instructions**
Dilute IV injection with glucose 5% only; incompatible with alkaline and chloride-containing solutions.

**Patient counseling**
This medication may cause dizziness or affect your vision; if you are affected, avoid driving or operating machinery.
In infants, separate doses from milk feeds as absorption may be reduced.

**Products**
FLECAINIDE AMP 10 MG/ML (AS ACETATE) 15 ML AMP (TAMBOCOR®)
FLECAINIDE TABS 100 MG (AS ACETATE) (TAMBOCOR®)

**LIDOCAINE**

**Mode of action**
Reduces automaticity of myocardial tissue with little effect on cardiac conduction. It has a mild negative inotropic effect and weak neuromuscular blocking activity.

**Indications**
Marketed: Treatment of serious ventricular arrhythmias
Accepted: Neuropathic pain (seek specialist advise)

**Contraindications**
Heart block, second or third degree (without pacemaker), Severe sinoatrial block (without pacemaker), Previous serious adverse reaction to lignocaine or amide local anaesthetics, Concurrent treatment with quinidine, flecainide, disopyramide, procainamide

**Specific considerations**
Bradycardia, hypovolaemia, cardiogenic shock, electrolyte disturbances (particularly hypo- or hyper-kalaemia):
increase risk of arrhythmia; correct before starting treatment if possible.
Atrial and supraventricular tachycardias: high incidence of hypotension.
Heart failure: may be exacerbated (clearance of lignocaine? also reduced and toxicity more likely).
Renal impairment: Active metabolites may accumulate during prolonged treatment in severe impairment; reduce
dose during prolonged infusion (>24 hours) or repeated IV doses.
Hepatic impairment: May accumulate during prolonged infusions due to decreased clearance in patients with severe
impairment or reduced hepatic blood flow (eg heart failure); consider halving the dose during prolonged infusion
(>24 hours) or repeated IV doses.
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Safe to use.

Adverse effects
Lignocaine has serious adverse effects including the potential to worsen arrhythmia (proarrhythmic effect).
Adverse effects are dose-related and are more frequent at infusion rates of 3 mg/minute or more.
Common: headache, dizziness, drowsiness, confusion, visual disturbances, tinnitus, tremor, paraesthesia
Infrequent: hypotension, bradycardia, arrhythmias, cardiac arrest, muscle twitching, convulsions, coma, respiratory
depression

Dosage
Adult, child
Initially, IV injection 1 mg/kg (in adults usually 75–100 mg) over 1–2 minutes, repeated after 5 minutes if necessary.
Maintenance, 10–50 micrograms/kg/minute IV infusion.

Administration instructions
Use undiluted for IV injection; compatible with glucose 5%, glucose/sodium chloride and sodium chloride 0.9%.

Products
LIDOCAINE VIAL/AMP 1 % (AS HCL) 10-50 ML (LIDOCAINE®, LIDOCAINE HCL®, LIDOCAINE VIAL/AMP 2 % (AS HCL) 10-50 ML (LIDOCAINE®, RICHMOND®)

PROPAFENONE

Indications
Ventricular arrhythmias; paroxysmal supraventricular tachyarrhythmias which include paroxysmal atrial flutter or
fibrillation and paroxysmal re-entrant tachycardias involving the AV node or accessory pathway, where standard
therapy ineffective or contra-indicated

Cautions
Heart failure; elderly; pacemaker patients; great caution in obstructive airways disease owing to beta-blocking
activity (contra-indicated if severe); hepatic impairment; renal impairment; pregnancy; breast-feeding.

Contra-indications
Uncontrolled congestive heart failure, cardiogenic shock (except arrhythmia induced), severe bradycardia, electrolyte
disturbances, severe obstructive pulmonary disease, marked hypotension; myasthenia gravis; unless adequately
paced avoid in sinus node dysfunction, atrial conduction defects, second degree or greater AV block, bundle branch
block or distal block

Side-effects
Antimuscarinic effects including constipation, blurred vision, and dry mouth; dizziness, nausea and vomiting, fatigue,
bitter taste, diarrhoea, headache, and allergic skin reactions reported; postural hypotension, particularly in elderly;
bradycardia, sino-atrial, atrioventricular, or intraventricular blocks; arrhythmogenic (pro-arrhythmic) effect; rarely
hypersensitivity reactions (cholestasis, blood disorders, lupus syndrome), seizures; myoclonus also reported

Dose
Body-weight 70 kg and over, initially 150 mg 3 times daily after food under direct hospital supervision with ECG
monitoring and blood pressure control (if QRS interval prolonged by more than 20%, reduce dose or discontinue
until ECG returns to normal limits); may be increased at intervals of at least 3 days to 300 mg twice daily and, if
necessary, to max. 300 mg 3 times daily; body-weight under 70 kg, reduce dose; elderly may respond to lower doses

Products
PROPAFENONE TABS 150 MG (AS HCL) (RYTMONORM®) PROPAFENONE TABS 300 MG (AS HCL) (RYTMONORM®)

VERAPAMIL

Mode of action
Block inward current of calcium into cells in vascular smooth muscle, myocardium and cardiac conducting system
via L-type calcium channels. Calcium channel blockers differ in their chemical nature, sites of action and therapeutic effects. Dihydropyridines act mainly on vascular smooth muscle to reduce peripheral vascular resistance, and have minimal effect on normal myocardial cells at therapeutic doses. Verapamil has greater cardiac effects, reducing contractility, heart rate and conduction with less effect on vascular smooth muscle. Diltiazem acts on both cardiac and vascular smooth muscle, but it has less effect on cardiac cells than verapamil.

**Indications**
- SVT with AV nodal re-entry, AF or atrial flutter (ventricular rate control), Hypertension, Angina, Supraventricular tachyarrhythmias, Prevention and treatment of ischaemic neurological deficits following subarachnoid haemorrhage

**Contraindications**
- Cardiogenic shock
- Severe bradycardia, sick sinus syndrome, second or third degree atrioventricular block (without pacemaker), hypotension (systolic BP <90 mm Hg)
- AF or atrial flutter complicating Wolff–Parkinson–White syndrome (verapamil)
- Wide complex ventricular tachycardia (IV administration)

**Specific considerations**
- Treatment with antiarrhythmics: increases risk of heart failure, bradycardia and proarrhythmic effect; avoid such combinations unless there is no alternative.
- Treatment with drugs which cause bradycardia: may further decrease heart rate and cause hypotension (the combination with beta-blockers is not recommended); monitor cardiac function.
- Heart failure, significantly impaired left ventricular function: risk of further depression of cardiac function.
- First degree atrioventricular block: risk of worsening.
- Angina: symptoms may be exacerbated when initiating treatment as a result of reflex cardiac stimulation (increased rate and contractility).
- Hepatic impairment: May require a reduction in dosage.
- Elderly: Start treatment at a lower dose.
- Pregnancy: may produce fetal hypoxia associated with maternal hypotension, primarily with short acting preparations; ADEC category C.
- Breastfeeding: Limited data available.

**Adverse effects**
Most listed adverse effects occur with all calcium channel blockers. Adverse effect profile varies between specific calcium channel blockers according to relative effects on vascular, myocardial and conducting tissue.
- Common: peripheral oedema, rash, headache, fatigue, dizziness, flushing, nausea, abdominal pain, gingival hyperplasia, bradycardia, constipation
- Infrequent: dihydropyridines, pulmonary oedema, hypotension, tachycardia, chest pain, dyspepsia, constipation, paraesthesia, muscle cramps, polyuria, rash, diltiazem, atrioventricular block, verapamil, elevation of hepatic enzymes, atrioventricular block, development or worsening of heart failure
- Rare: parkinsonism, dihydropyridines, cerebral and myocardial ischaemia (following excessive fall in BP) diltiazem, hypersensitivity reactions including erythema multiforme and exfoliative dermatitis, hepatitis, gingival hyperplasia, verapamil, gynaecomastia, hepatitis, gingival hyperplasia

**Dosage**

**Arrhythmias**
- Adult, initially IV injection 5 mg (over 2–3 minutes) repeated after 5–10 minutes as required. Maintenance, IV infusion 5–10 mg/hour, up to a maximum of 100 mg daily; or oral 120–480 mg daily.
- Child, IV injection 0.1–0.3 mg/kg to a maximum of 5 mg; repeat after 30 minutes or follow with infusion of 1.25–5 micrograms/kg/minute; oral 1–3 mg/kg/dose 3 times daily.
- Conventional product: Angina, hypertension, initially oral 80 mg 2–3 times daily; maintenance dose, 160 mg 2–3 times daily.
- Controlled release product: Angina, initially 180–240 mg once daily, increasing if necessary to 240 mg once or twice daily. Hypertension, initially 120–180 mg once daily, increasing if necessary to 240 mg once or twice daily.

**Administration instructions**
- Give IV injections slowly under continuous ECG monitoring over 2–3 minutes; rapid IV administration may result in hypotension, bradycardia, heart block and asystole.

**Patient counselling**
Verapamil may increase the effects of alcohol so that you are more easily affected and the effects last longer. Limit
 Evidence that these drugs have
and atrioventricular node
ose
Beta
potential duration and have specific indications.
conduction, and prolong atrial refractory periods; in addition, some beta
Antiarrhythmic properties due to antisympathetic effect; depress sinus node function a
contractility.
Antianginal effect due to reduction in left ventricular work and oxygen use, resulting from decrease in heart rate and
effect and reduced r
Antihypertensive effect by reducing cardiac output without reflex increase in peripheral vascular resistance; CNS
Competitively block beta receptors in heart, peripheral vasculature, bronchi, pancreas, and liver.
Mode of action
hypoglycaemia (see above) may be preferable and beta
tolerance and interfere with metabolic and autonomic responses to hypoglycaemia. Cardioselective beta
Beta
anti-adrenergic activity; they tend to cause less bradycardia than the other beta-blockers and may also cause less
coldness of the extremities.
Some beta-blockers are lipid soluble and some are water soluble. Atenolol, celiprolol, nadolol, and sotalol are the
most water-soluble; they are less likely to enter the brain, and may therefore cause less sleep disturbance and
nightmares. Water-soluble beta-blockers are excreted by the kidneys; they accumulate in renal impairment and
dosage reduction is therefore often necessary.
Beta-blockers with a relatively short duration of action have to be given two or three times daily. Many of these are,
however, available in modified-release formulations so that administration once daily is adequate for hypertension.
For angina twice-daily treatment may sometimes be needed even with a modified-release formulation. Some beta-
blockers such as atenolol, bisoprolol, carvedilol, celiprolol, and nadolol have an intrinsically longer duration of
action and need to be given only once daily.
Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in patients with second-
third-degree heart block. Beta-blockers should also be avoided in patients with worsening unstable heart failure; care
is required when initiating a beta-blocker in those with stable heart failure (Sotalol may prolong the QT interval, and
it occasionally causes life-threatening ventricular arrhythmias (important: particular care is required to avoid
hypokalaemia in patients taking sotalol).
Labetalol, celiprolol, carvedilol and nebivolol are beta-blockers which have, in addition, an arteriolar vasodilating
action, by diverse mechanisms, and thus lower peripheral resistance. There is no evidence that these drugs have
important advantages over other beta-blockers in the treatment of hypertension.
Beta-blockers may precipitate asthma and this effect can be dangerous. Beta-blockers should be avoided in patients
with a history of asthma or bronchospasm; if there is no alternative, a cardioselective beta-blocker may be used with
extreme caution under specialist supervision. Atenolol, bisoprolol, metoprolol, nebivolol and (to a lesser extent)
acebutolol, have less effect on the beta2 (bronchial) receptors and are, therefore, relatively cardioselective, but they
are not cardiospecific. They have a lesser effect on airways resistance but are not free of this side-effect.
Beta-blockers are also associated with fatigue, coldness of the extremities (may be less common with those with ISA,
and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers, see above).
Beta-blockers are not contra-indicated in diabetes; however, they can lead to a small deterioration of glucose
tolerance and interfere with metabolic and autonomic responses to hypoglycaemia. Cardioselective beta-blockers
(see above) may be preferable and beta-blockers should be avoided altogether in those with frequent episodes of
hypoglycaemia.
Mode of action
Competitively block beta receptors in heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver.
Antihypertensive effect by reducing cardiac output without reflex increase in peripheral vascular resistance; CNS
effect and reduced renin secretion may also contribute.
Antiarrhythmic effect due to reduction in left ventricular work and oxygen use, resulting from decrease in heart rate and
contractility.
Antiarrhythmic properties due to antisympathetic effect; depress sinus node function and atrioventricular node
conduction, and prolong atrial refractory periods; in addition, some beta-blockers (eg sotalol) prolong action
potential duration and have specific indications.
Beta1-selective beta-blockers have a higher affinity for beta1 receptors in the heart, with less effect on beta2 receptors

02.04 BETA-ADRENOCEPTOR BLOCKING DRUGS
Beta-adrenoceptor blocking drugs (beta-blockers) competitively block the beta-adrenoreceptors in the heart,
peripheral vasculature, bronchi, pancreas, and liver.
Many beta-blockers are now available and in general they are all equally effective. There are, however, differences
between them which may affect choice in treating particular diseases or individual patients.
Intrinsic sympathomimetic activity (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate
as well as to block adrenergic receptors. Oxprenolol, pindolol, acebutolol and celiprolol have intrinsic
sympathomimetic activity; they tend to cause less bradycardia than the other beta-blockers and may also cause less
coldness of the extremities.
Products
VERAPAMIL AMPS 5 MG/AMP (AS HCL) 2 ML AMP (NOT REGISTERED)
VERAPAMIL TABS 80 MG (AS HCL, SCORED) (ISOPTIN®)
VERAPAMIL TABS 240 MG (AS HCL) (ISOPTIN SR®)

Practice points
- dihydropyridine-induced peripheral oedema does not require treatment with diuretics, which may put
patient at risk of volume depletion

Your alcohol intake until you know whether you are affected like this.
in bronchi and peripheral vasculature; beta₁-selectivity diminishes with higher doses.

Some beta-blockers (eg oxprenolol, pindolol) have intrinsic sympathomimetic activity (ISA); they have the capacity to stimulate (partial agonist activity) and block beta receptors.

Some beta-blockers with mixed beta-blocking and alpha₁-blocking ability (eg labetalol, carvedilol) provide additional arterial vasodilating action.

**Indications**

**Marketed:** Hypertension, Angina (stable and unstable), Arrhythmias, Control of symptoms (tachycardia, tremor) in anxiety and hyperthyroidism (propranolol), Fallot's tetralogy (propranolol), MI (atenolol, metoprolol, propranolol)

Prevention of migraine (metoprolol, propranolol), Essential tremor (propranolol), Phaeochromocytoma, with concurrent alpha-blocker treatment (propranolol), Glaucoma, topical. Heart failure, as an adjunct to conventional treatments (bisoprolol, carvedilol, controlled release metoprolol)

**Accepted:** Portal hypertension and prevention of oesophageal variceal bleeding (propranolol)

**Contraindications**

Reversible airways disease (eg asthma, COPD)

Bradycardia (45–50 beats/minute), sick sinus syndrome, second or third degree atrioventricular block, shock (cardiogenic and hypovolaemic), severe hypotension; uncontrolled heart failure

**Specific considerations**

Diabetes: beta-blockers may mask important signs of acute hypoglycaemia (eg tachycardia, tremor), and increase incidence and severity of hypoglycaemia but data are conflicting; beta₁-selective beta-blockers (eg atenolol), are preferable as they have been shown to be safe and effective in patients with type 2 diabetes.

Severe peripheral vascular disease, Raynaud's syndrome: may impair peripheral circulation and exacerbate symptoms.

Hyperthyroidism: may mask clinical signs, eg tachycardia.

Phaeochromocytoma: may aggravate hypertension; alpha-blockers should be given first.

Any anaphylactic reaction: patients may be unresponsive to usual doses of adrenaline.

Vasospastic angina: risk of exacerbating coronary artery spasm.

Myasthenic symptoms: may be exacerbated.

Treatment with drugs which cause bradycardia: may further decrease heart rate and cause heart block and hypotension; avoid combination with verapamil; monitor cardiac function with other combinations.

Renal impairment: Use beta-blockers with predominantly hepatic elimination, eg metoprolol, or reduce dosage of beta-blockers with predominantly renal elimination, eg atenolol.

Hepatic impairment: Use beta-blockers with predominantly renal elimination, eg atenolol; dosage reduction may be required for beta-blockers with predominantly hepatic elimination.

Surgery: Increased risk of bradycardia and hypotension; however beta-blockers should not be stopped suddenly, especially in patients with known ischaemic heart disease.

Pregnancy: These agents may cause pharmacological effects such as bradycardia in the fetus and newborn infant; ADEC category C.

Breastfeeding: Metoprolol, labetalol and propranolol are preferred to atenolol as they are more extensively protein bound and therefore less likely to be excreted in breast milk.

**Adverse effects**

Common: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension, orthostatic hypotension (carvedilol, labetalol), heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, alteration of glucose and lipid metabolism, oedema (carvedilol)

Infrequent: rash, exacerbation of psoriasis, impotence, muscle cramp, acute urinary retention, nasal congestion, scalp tingling (labetalol)

Rare: hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest, hepatic injury (atenolol, labetalol, carvedilol)

**Comparative information**

Beta-blockers are marketed for a number of cardiovascular indications. They have been shown to reduce cardiovascular morbidity and mortality in hypertension, angina and MI (acute and long term treatment).

Choice between individual agents may be determined by their marketed indications and pharmacological differences. Beta₁-selective beta-blockers (eg atenolol, metoprolol) may produce less bronchospasm, less peripheral vasoconstriction and less alteration of glucose and lipid metabolism. They may be preferred in peripheral vascular disease, Raynaud's syndrome, diabetes or mild-to-moderate reversible airways disease.

Beta-blockers with intrinsic sympathomimetic activity (eg oxprenolol, pindolol) may cause less bradycardia and less coldness of extremities; however, they may be less effective in the treatment of angina and tachyarrhythmias. They
have not been found to benefit patients after MI. Some beta-blockers (eg labetalol, carvedilol) have additional vasodilating properties through alpha₁-blockade. The clinical relevance of these properties is not well established. A number of beta-blockers, including bisoprolol, controlled release metoprolol and carvedilol, reduce mortality and risk of hospitalisation in patients with stabilised heart failure when used with an ACE inhibitor, loop diuretic and digoxin. Less lipid soluble beta-blockers (eg atenolol) may be less likely to enter the brain and may cause fewer sleep disturbances and nightmares. Beta-blockers that have predominantly hepatic elimination may be preferred in patients with renal impairment and vice versa. Esmolol and sotalol are approved for the treatment of arrhythmias only; esmolol has a very short duration of action and is used IV for the short term treatment of AF and atrial flutter, sinus tachycardia and hypertension in the perioperative period. Betaxolol, levobunolol and timolol are used topically in glaucoma.

**Patient counselling**
This medicine may cause dizziness or tiredness especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
Do not stop taking this medicine suddenly unless your doctor tells you to.

**Practice points**
- when stopping treatment reduce dosage gradually (over 2 weeks or 4–6 weeks if the patient has been treated for many years); abrupt withdrawal may exacerbate angina, or precipitate rebound hypertension, MI or ventricular arrhythmias

### 02.04.01 Cardioselective

**ATENOLOL**

**Mode of action**
Competitively block beta receptors in heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver. Antihypertensive effect by reducing cardiac output without reflex increase in peripheral vascular resistance; CNS effect and reduced renin secretion may also contribute. Antianginal effect due to reduction in left ventricular work and oxygen use, resulting from decrease in heart rate and contractility. Antiarrhythmic properties due to antisympathetic effect; depress sinus node function and atrioventricular node conduction, and prolong atrial refractory periods. Beta₁-selective beta-blockers have a higher affinity for beta₁ receptors in the heart, with less effect on beta₂ receptors in bronchi and peripheral vasculature; beta₁-selectivity diminishes with higher doses.

**Indications**
Marketed: Hypertension, Tachyarrhythmias, MI, Angina (stable and unstable).
Accepted: Prevention of migraine.

**Contraindications**
Reversible airways disease (eg asthma, COPD) Bradycardia (45–50 beats/minute), sick sinus syndrome, second or third degree atrioventricular block, shock (cardiogenic and hypovolaemic), severe hypotension; uncontrolled heart failure

**Specific considerations**
Diabetes: beta-blockers may mask important signs of acute hypoglycaemia (eg tachycardia, tremor), and increase incidence and severity of hypoglycaemia but data are conflicting; beta₁-selective beta-blockers (eg atenolol), are preferable as they have been shown to be safe and effective in patients with type 2 diabetes. Severe peripheral vascular disease, Raynaud's syndrome: may impair peripheral circulation and exacerbate symptoms.
Hyperthyroidism: may mask clinical signs, eg tachycardia.
Phaeochromocytoma: may aggravate hypertension; alpha-blockers should be given first.
Any anaphylactic reaction: patients may be unresponsive to usual doses of adrenaline.
Vasospastic angina: risk of exacerbating coronary artery spasm.
Myasthenic symptoms: may be exacerbated.
Treatment with drugs which cause bradycardia: may further decrease heart rate and cause heart block and hypotension; avoid combination with verapamil; monitor cardiac function with other combinations.
Renal impairment: May accumulate; lower dosage may be required.

Hepatic impairment: Use beta-blockers with predominantly renal elimination, eg atenolol; dosage reduction may be required for beta-blockers with predominantly hepatic elimination.

Surgery: Increased risk of bradycardia and hypotension; however beta-blockers should not be stopped suddenly, especially in patients with known ischaemic heart disease.

Pregnancy: may cause pharmacological effects such as bradycardia in the fetus and newborn infant; ADEC category C.

Breastfeeding: Metoprolol, labetalol and propranolol are preferred to atenolol as they are more extensively protein bound and therefore less likely to be excreted in breast milk.

**Adverse effects**

Common: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension, heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, alteration of glucose and lipid metabolism.

Infrequent: rash, exacerbation of psoriasis, impotence, muscle cramp, acute urinary retention, nasal congestion, scalp tingling (labetalol)

Rare: hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest, hepatic injury.

**Dosage**

- Hypertension, angina, migraine prevention: 25–100 mg once daily.
- Tachyarrhythmias: 50–100 mg once daily.
- Myocardial infarction: Maintenance, 50 mg daily.
- Renal impairment: Severe, 50 mg on alternate days; or 100 mg twice a week., Moderate, 50 mg daily; or 100 mg on alternate days.

**Patient counselling**

This medicine may cause dizziness or tiredness especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.

Do not stop taking this medicine suddenly unless your doctor tells you to.

**Practice points**

- when stopping treatment reduce dosage gradually (over 2 weeks or 4–6 weeks if the patient has been treated for many years); abrupt withdrawal may exacerbate angina, or precipitate rebound hypertension, MI or ventricular arrhythmias

**Products**

- ATENOLOL TABS 50 MG (APO-ATENOLOL®, ATELOL®, BLOKIUM®, HYPOTEN®, LOTEN®, TENOLOL®, TENOPRESS®, TENORMIN®)
- ATENOLOL TABS 100 MG (APO-ATENOLOL®, ATELOL®, BLOKIUM®, HYPOTEN®, LOTEN®, TENOLOL®, TENOPRESS®, TENORMIN®)

**BETAXOLOL**

**Mode of action**

Reduces aqueous humour formation, probably by blockade of the beta receptors on the ciliary epithelium.

Betaxolol is a cardioselective beta blocker. It is reported to lack intrinsic sympathomimetic activity and to have little membrane-stabilising activity.

Betaxolol is used as the hydrochloride in the management of hypertension

**Indications**

Mangement of hypertension., angina pectoris, glaucoma

**Contraindications**

- Reversible airways disease, like asthma (may be used with care)
- Bradyarrhythmia, second or third degree atrioventricular block, Shock

**Specific considerations**

Potentially the same as for systemic beta-blockers.

Treatment with systemic nonselective beta-blocker: reduces intraocular pressure. Adding topical beta-blocker when taking a systemic beta-blocker offers some additional pressure reduction but may increase systemic adverse effects. combination with verapamil: potential for profound bradycardia; avoid combination.

Surgery: Theoretical increased risk of bradycardia and hypotension during surgery.

Elderly: Systemic adverse effects, eg hypotension (may cause falls), are more common.

Children: May cause apnoea in neonates and bradycardia in children.

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Pregnancy: May cause fetal bradycardia; ADEC category C.
Breastfeeding: Unlikely to cause adverse effects at usual doses.

**Precautions**

Administer cautiously in compensated heart failure and monitor for a worsening of the condition. Avoid abrupt discontinuation in patients with history of CAD. Slowly wean while monitoring for signs and symptoms of ischemia. Use cautiously with concurrent use of beta-blockers and either verapamil or diltiazem; bradycardia or heart block can occur. Use with caution in patients with PVD (can aggravate arterial insufficiency). In general beta-blockers should be avoided in patients with bronchospastic disease with close monitoring. Use cautiously in diabetics because it can mask prominent hypoglycemic symptoms. Can cause fetal harm when administered in pregnancy. Dosage adjustment required in severe renal impairment and those on dialysis. Use carefully with anesthetic agents which decrease myocardial function.

**Adverse effects**

The most important adverse effects are systemic.
Common: stinging on instillation (especially betaxolol solution), bradycardia.
Infrequent: decreased corneal sensation, hypotension, syncope, impotence, decreased libido, fatigue, confusion

**Dosage**

In hypertension betaxolol hydrochloride is given in initial doses of 10 to 20 mg as a single daily dose by mouth; doses may be increased if necessary after 1 to 2 weeks according to response, to 40 mg daily. Similar doses are used in angina pectoris.
Initial doses of 5 to 10 mg daily are suggested for elderly patients. Reduced dosages should also be used in patients with severe renal impairment.

**Products**

BETAXOLOL TABS 10 MG (AS HCL) (KERLON®)
BETAXOLOL TABS 20 MG (AS HCL) (KERLON®)

**BISOPROLOL**

**Mode of action**

Competitively block beta receptors in heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver. Antihypertensive effect by reducing cardiac output without reflex increase in peripheral vascular resistance; CNS effect and reduced renin secretion may also contribute. Antiarrhythmic effect due to reduction in left ventricular work and oxygen use, resulting from decrease in heart rate and contractility. Antiarrhythmic properties due to antisympathetic effect; depress sinus node function and atrioventricular node conduction, and prolong atrial refractory periods; in addition, some beta-blockers (eg sotalol) prolong action potential duration and have specific indications.
Beta1-selective beta-blockers have a higher affinity for beta1 receptors in the heart, with less effect on beta2 receptors in bronchi and peripheral vasculature; beta1-selectivity diminishes with higher doses.

**Indications**

Stable moderate-to-severe heart failure in addition to ACE inhibitors, diuretics, and optionally digoxin
Marketed: Hypertension, Angina (stable and unstable), Cardiac arrhythmias. Glaucoma, topical, Heart failure, as an adjunct to conventional treatments

**Contraindications**

Reversible airways disease (eg asthma, COPD)
Bradycardia (45–50 beats/minute), sick sinus syndrome, second or third degree atrioventricular block, shock (cardiogenic and hypovolaemic), severe hypotension; uncontrolled heart failure

**Specific considerations**

Diabetes: beta-blockers may mask important signs of acute hypoglycaemia (eg tachycardia, tremor), and increase incidence and severity of hypoglycaemia but data are conflicting; beta1-selective beta-blockers (eg atenolol), are preferable as they have been shown to be safe and effective in patients with type 2 diabetes.
Severe peripheral vascular diseases, Raynaud’s syndrome: may impair peripheral circulation and exacerbate symptoms.
Hyperthyroidism: may mask clinical signs, eg tachycardia.
Phaeochromocytoma: may aggravate hypertension; alpha-blockers should be given first.
Any anaphylactic reaction: patients may be unresponsive to usual doses of adrenaline.
Vasospastic angina: risk of exacerbating coronary artery spasm.

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Myasthenic symptoms: may be exacerbated.
Treatment with drugs which cause bradycardia: may further decrease heart rate and cause heart block and hypotension; avoid combination with verapamil; monitor cardiac function with other combinations.
Renal impairment: No dose reduction required up to 10 mg daily.
Hepatic impairment: Use beta-blockers with predominantly renal elimination.
Surgery: Increased risk of bradycardia and hypotension; however beta-blockers should not be stopped suddenly, especially in patients with known ischaemic heart disease.
Pregnancy: may cause pharmacological effects such as bradycardia in the fetus and newborn infant; ADEC category C.
Breastfeeding: no data available.

**Adverse effects**
Common: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension, heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, alteration of glucose and lipid metabolism,
Infrequent: rash, exacerbation of psoriasis, impotence, muscle cramp, acute urinary retention, nasal congestion
Rare: hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest.

**Dosage**
Initially, 1.25 mg once daily for 1 week; increase dose if well tolerated according to the following steps: 2.5 mg once daily for a week, then 3.75 mg once daily for a week, then 5 mg once daily for 4 weeks, then 7.5 mg once daily for 4 weeks, then 10 mg once daily for maintenance. Slower dose titration may be appropriate in some patients.

**Patient counseling**
This medicine may cause dizziness or tiredness especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
Do not stop taking this medicine suddenly unless your doctor tells you to.

**Practice points**
- before starting treatment, optimise conventional treatments; ensure that patients with severe heart failure are well stabilised with sitting systolic BP >85 mm Hg, without peripheral oedema, new pulmonary rales or ascites, recent unstable angina, cardiac surgery or ventricular arrhythmia
- reduce dose if heart rate is <55 beats/minute
- treat transient worsening of heart failure with increased doses of diuretics; temporarily withdraw bisoprolol if necessary
- treat hypotension by reducing the dose of diuretics and other vasodilating drugs first; reduce dose of bisoprolol if necessary
- do not stop bisoprolol abruptly; halve dose each week
- when stopping treatment reduce dosage gradually (over 2 weeks or 4–6 weeks if the patient has been treated for many years); abrupt withdrawal may exacerbate angina, or precipitate rebound hypertension, MI or ventricular arrhythmias

**Products**
**BISOPROLOL TABS 5 MG (AS FUMARATE) (B-COR®, CONCOR®, BISOPROL®)**
**BISOPROLOL TABS 10 MG (AS FUMARATE) (B-COR®, CARDIOSAFE®, CONCOR®, BISOPROL®, FORCICOR®)**

**METOPROLOL**

**Mode of action :**
Same as Bisoprolol

**Indications**
Hypertension, Angina, Tachyarrhythmias, MI, Prevention of migraine, Stable heart failure with an ACE inhibitor, diuretics, and optional digoxin (controlled released product only)
Marketed: Hypertension, Angina (stable and unstable), Cardiac arrhythmias, MI. Prevention of migraine Glaucoma, topical, Heart failure, as an adjunct to conventional treatments

**Contraindications**
Reversible airways disease (e.g. asthma, COPD)
Bradycardia (45–50 beats/minute), sick sinus syndrome, second or third degree atrioventricular block, shock (cardiogenic and hypovolaemic), severe hypotension; uncontrolled heart failure

**Specific considerations**
Hepatic impairment: May require a lower dosage.
Adverse effects
Common: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud’s syndrome, bradycardia, hypotension, heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, alteration of glucose and lipid metabolism.
Infrequent: rash, exacerbation of psoriasis, impotence, muscle cramp, acute urinary retention, nasal congestion.
Rare: hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest.

Dosage
Hypertension: Oral, initially, 50–100 mg once daily for 1 week. Maintenance 50–100 mg once or twice daily.
Angina: Oral, initially, 25–50 mg twice daily. Maintenance 50–100 mg 2–3 times daily.
Tachyarrhythmias: IV, 5 mg (1 mg/minute) repeated at 5-minute intervals up to a maximum of 20 mg. Oral, 50–100 mg 2–3 times daily.
Myocardial infarction: Initially, 5 mg IV at 5-minute intervals to a total of 15 mg, then 25–50 mg orally every 6 hours for 48 hours. Maintenance, oral 50–100 mg twice daily.
Prevention of migraine: Oral, 50–75 mg twice daily.
Heart failure: Controlled release tablet, initially, 23.75 mg once daily for a minimum of 2 weeks (halve dose in patients with NYHA III or IV heart failure for first week). Increase dose (if well tolerated) as follows, remaining at each dose level for a minimum of 2 weeks: 47.5 mg once daily, then 95 mg once daily, then 190 mg once daily for maintenance. Slower dose titration may be appropriate in some patients.

Patient counselling
Controlled release tablets may be broken in half or swallowed whole; do not chew or crush them.
This medicine may cause dizziness or tiredness especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
Same as Bisoprolol

Products
METOPROLOL TABS 100 MG (AS TARTRATE OR SUCCINATE) (BETALOC ZOK®, LOPRESOR®)

NEBIVOLOL

Indications
Essential hypertension

Cautions
See under Propranolol Hydrochloride; reduce dose in renal impairment; elderly

Contra-indications
See under Propranolol Hydrochloride; hepatic impairment

Side-effects
See under Propranolol Hydrochloride; oedema, headache, depression, visual disturbances, paraesthesia, impotence

Dose
5 mg daily; elderly initially 2.5 mg daily, increased if necessary to 5 mg daily

Products
NEBIVOLOL TABS 5 MG (AS HCL) (NEBILET®)

02.04.02 Non Cardioselective

CARVEDILOL

Mode of action
Competitively block beta receptors in heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver.
Antihypertensive effect by reducing cardiac output without reflex increase in peripheral vascular resistance; CNS effect and reduced renin secretion may also contribute.
Antianginal effect due to reduction in left ventricular work and oxygen use, resulting from decrease in heart rate and contractility.
Antiarrhythmic properties due to antisympathetic effect; depress sinus node function and atrioventricular node conduction, and prolong atrial refractory periods.
Beta₁-selective beta-blockers have a higher affinity for beta₁ receptors in the heart, with less effect on beta₂ receptors in bronchi and peripheral vasculature; beta₁-selectivity diminishes with higher doses. It provide additional arteriolar vasodilating action.
Indications
Hypertension: Stable mild-to-severe heart failure, as an adjunct to conventional treatments (eg diuretics, digoxin, ACE inhibitors and vasodilators)
Marketed: Hypertension, Angina (stable and unstable), Cardiac arrhythmias, Glaucoma, topical, Heart failure, as an adjunct to conventional treatments.

Contraindications
Reversible airways disease (eg asthma, COPD)
Bradydcardia (45–50 beats/minute), sick sinus syndrome, second or third degree atioventricular block, shock (cardiogenic and hypovolaemic), severe hypotension; uncontrolled heart failure

Specific considerations
Hepatic impairment: Avoid use in severe impairment.

Same as Bisoprolol

Adverse effects
Common: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension, heart failure, heart block, fatiguedixiness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, alteration of glucose and lipid metabolism, oedema
Infrequent: rash, exacerbation of psoriasis, impotence, muscle cramp, acute urinary retention, nasal congestion, Rare: hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest, hepatic injury

Dosage
Hypertension: Initially, 12.5 mg once daily for 2 days. Maintenance, 25 mg once daily, increased if necessary at intervals of at least 2 weeks up to a maximum of 50 mg once daily or in 2 divided doses.
Heart failure: Initially, 3.125 mg twice daily for 2 weeks; increase at intervals of at least 2 weeks to 6.25 mg twice daily, then 12.5 mg twice daily, then 25 mg twice daily (maximum in patients <85 kg with mild-to-moderate heart failure and in all patients with severe heart failure) or 50 mg twice daily (maximum in patients >85 kg); use the highest dose tolerated by the patient. Slower dose titration may be appropriate in some patients.

Patient counselling
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.
This medicine may cause dizziness or tiredness especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
Same as Bisoprolol

Products
CARVEDILOL TABS 6.25 MG (CARVIDOL®, DILATREN®)
CARVEDILOL TABS 25 MG (CARVIDOL®, DILATREN®)

NADOLOL

Indications
Nadolol is a non-cardioselective beta blocker. It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity. Nadolol is used in the management of hypertension, angina pectoris, and cardiac arrhythmias. It is also used in the management of hyperthyroidism and in the prophylactic treatment of migraine

Contra-indications
See under Propranolol Hydrochloride

Side-effects
See under Propranolol Hydrochloride

Dose
Hypertension, 80 mg daily, increased at weekly intervals if required; max. 240 mg daily
Angina, 40 mg daily, increased at weekly intervals if required; usual max. 160 mg daily
Arrhythmias, initially 40 mg daily, increased to 160 mg if required; reduce to 40 mg if bradycardia occurs
Migraine prophylaxis, initially 40 mg daily, increased by 40 mg at weekly intervals; usual maintenance dose 80–160 mg daily
Thyrotoxicosis (adjunct), 80–160 mg daily
Doses of 40 to 160 mg once daily are used in migraine prophylaxis.
In the management of hyperthyroidism, doses of 80 to 160 mg once daily have been given; most patients are reported to require the higher dose. Patients with renal impairment may require a reduction in dose.

**Products**

**NADOLOL TABS 80 MG (COGARD®)**

**PROPRANOLOL**

**Mode of action**

Competitively block beta receptors in heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver. Antihypertensive effect by reducing cardiac output without reflex increase in peripheral vascular resistance; CNS effect and reduced renin secretion may also contribute.

Antiarrhythmic properties due to antisympathectic effect; depress sinus node function and atrioventricular node conduction, and prolong atrial refractory periods.

Beta₁-selective beta-blockers have a higher affinity for beta₁ receptors in the heart, with less effect on beta₂ receptors in bronchi and peripheral vasculature; beta₁-selectivity diminishes with higher doses.

**Indications**

Marketed: Hypertension, Angina (stable and unstable), Cardiac arrhythmias, Control of symptoms (tachycardia, tremor) in anxiety and hyperthyroidism, Fallot's tetralogy, MI, Prevention of migraine, Essential tremor, Phaeochromocytoma, with concurrent alpha-blocker treatment, Glaucoma, topical.

Accepted: Portal hypertension and prevention of oesophageal variceal bleeding.

**Contraindications**

Reversible airways disease (eg asthma, COPD)

Bradyarrhythmia (45–50 beats/minute), sick sinus syndrome, second or third degree atrioventricular block, shock (cardiogenic and hypovolaemic), severe hypotension; uncontrolled heart failure.

**Specific considerations**

Diabetes: beta-blockers may mask important signs of acute hypoglycaemia (eg tachycardia, tremor), and increase incidence and severity of hypoglycaemia but data are conflicting; beta₁-selective beta-blockers, are preferable as they have been shown to be safe and effective in patients with type 2 diabetes.

Severe peripheral vascular disease, Raynaud's syndrome: may impair peripheral circulation and exacerbate symptoms.

Hyperthyroidism: may mask clinical signs, eg tachycardia.

Phaeochromocytoma: may aggravate hypertension; alpha-blockers should be given first.

Any anaphylactic reaction: patients may be unresponsive to usual doses of adrenaline.

Vasospastic angina: risk of exacerbating coronary artery spasm.

Myasthenic symptoms: may be exacerbated.

Treatment with drugs which cause bradycardia: may further decrease heart rate and cause heart block and hypotension; avoid combination with verapamil; monitor cardiac function with other combinations.

Renal impairment: Use beta-blockers with predominantly hepatic elimination, eg metoprolol, or reduce dosage of beta-blockers with predominantly renal elimination.

Hepatic impairment: May require a lower dosage.

Surgery: Increased risk of bradycardia and hypotension; however beta-blockers should not be stopped suddenly, especially in patients with known ischaemic heart disease.

Pregnancy: These agents may cause pharmacological effects such as bradycardia in the fetus and newborn infant; ADEC category C.

Breastfeeding: it is extensively protein bound and therefore less likely to be excreted in breast milk.

**Adverse effects**

Common: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension, heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, alteration of glucose and lipid metabolism.

Infrequent: rash, exacerbation of psoriasis, impotence, muscle cramp, acute urinary retention, nasal congestion.

Rare: hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest.

**Dosage**

**Adult**

Hypertension, initially 20–40 mg twice daily, increased by the same amount each week. Maintenance, 120–320 mg daily in 2–3 divided doses.
Angina, essential tremor, initially 40 mg 2–3 times daily, increased by the same amount each week. Maintenance, 120–320 mg daily in 2–3 divided doses.
Tachyarrhythmias (including hyperthyroidism and anxiety), 10–40 mg 3–4 times daily.
MI, initially 40 mg 4 times daily for 2–3 days. Maintenance, 80 mg twice daily.
Prevention of migraine, initially 40 mg twice daily. Maintenance, 80–160 mg daily.
Phaeochromocytoma, 60 mg daily in divided doses for 3 days preoperatively. Maintenance, 30 mg daily in 2–3 divided doses.
Portal hypertension, initially 40 mg twice daily, increase to 80 mg twice daily according to heart rate. Maximum, 160 mg twice daily.
Child
Tachyarrhythmias (including hyperthyroidism and anxiety), 0.25–0.5 mg/kg 3–4 times daily.
Fallot's tetralogy, up to 1 mg/kg 3–4 times daily as required.
Prevention of migraine (>7 years), initially 10 mg once or twice daily, increased up to 2 mg/kg daily in divided doses.

Patient Counselling
This medicine may cause dizziness or tiredness especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
- when stopping treatment reduce dosage gradually (over 2 weeks or 4–6 weeks if the patient has been treated for many years); abrupt withdrawal may exacerbate angina, or precipitate rebound hypertension, MI or ventricular arrhythmias

Products
PROPRANOLOL AMPS 1 MG/AMP (AS HCL) 1 ML AMP (NOT REGISTERED)
PROPRANOLOL TABS 10 MG (AS HCL) (INDERAL®, INDICARDIN®)
PROPRANOLOL TABS 40 MG (AS HCL) (INDERAL®, INDICARDIN®, ATENSIN®)
PROPRANOLOL TABS 80 MG (AS HCL) (INDERAL LA®, INDICARDIN®)
PROPRANOLOL CAPS 160 MG (AS HCL) (INDERAL LA®)

02.05 DRUGS AFFECTING THE RENIN-ANGIO-TENSIN SYSTEM AND SOME OTHER ANTIHYPERTENSIVE DRUGS

HYPERTENSION
Rationale for drug use
Reduce premature cardiovascular morbidity and mortality from cerebrovascular disease, coronary artery disease, heart failure and aortic aneurysm, and reduce microvascular disease affecting the brain, kidney and retina.

Before starting treatment
Confirm diagnosis of hypertension with multiple readings across time and correct size cuff; consider possibility of 'white coat effect' on BP.
Consider secondary causes for hypertension.
Consider lifestyle interventions. Each lifestyle intervention has the potential to reduce BP equivalent to that of 1 standard dose of an antihypertensive drug in appropriately selected patients. Consider weight loss, salt and alcohol reduction, exercise, and diet high in fresh fruit, vegetables and low in saturated fats.

Cardiovascular risk
Assess overall cardiovascular risk. Basing treatment decision on assessment of the patient's overall cardiovascular risk is likely to be more effective than on BP alone. Cardiovascular risk is stratified according to level of BP and presence of other risk factors, target organ disease and associated clinical conditions.

Drug choice
Five drug classes are commonly used for lowering BP: thiazide diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, and calcium channel blockers.
All have similar efficacy as monotherapy in lowering BP and in reducing cardiovascular mortality. Low dose thiazide diuretics are first line treatment as they are at least as effective as all other drug classes and are the least expensive.

Thiazide diuretics
First line treatment in hypertension unless there is a contraindication or a specific indication for another drug.
Particularly indicated for hypertension in elderly, a contra-indication is gout
Risk of metabolic adverse effects (raised blood glucose and cholesterol concentrations) is mainly associated with use
of high doses; clinical significance of metabolic changes observed with low doses is questionable as they do not lead to a higher rate of cardiovascular complications.
Risk of hypokalaemia; monitor potassium concentration.

**Beta-blockers**
Seem to be less effective than thiazide diuretics in people >65 years.
Indications include myocardial infarction, angina. Compelling contra-indications include asthma, heart block
Atenolol, metoprolol and propranolol have been shown to reduce cardiovascular morbidity and mortality in patients following MI and are first line treatment in this setting.
Contraindicated in severe asthma or heart block.
Bradyarrhythmia and nightmares are adverse effects that may limit therapy.

**ACE inhibitors**
indications include heart failure, left ventricular dysfunction and diabetic nephropathy; contra-indications include renovascular disease and pregnancy
Are not shown to be superior to diuretics in terms of cardiovascular prevention or overall incidence of adverse effects (ALLHAT trial).
First line treatment in patients with heart failure or with left ventricular dysfunction, in particular following MI.
First line treatment in patients with type 1 diabetes and microalbuminuria or proteinuria. Ramipril is also indicated for prevention of progressive renal failure in patients with persistent proteinuria.
Risk of hyperkalaemia; avoid combinations with potassium, potassium-sparing diuretics and NSAIDs (including selective COX-2 inhibitors).
Contraindicated in patients with bilateral renal artery stenosis, in pregnancy and with a history of angioedema.

**Angiotensin II antagonists**
are alternatives for those who cannot tolerate ACE inhibitors because of persistent dry cough, but they have the same contra-indications as ACE inhibitors
Losartan has been shown to reduce cardiovascular morbidity and mortality slightly more than atenolol in patients with both hypertension and left ventricular hypertrophy, especially in those with diabetes.
Angiotensin II antagonists may be used as an alternative to first line treatments especially in patients with heart failure, diabetes or proteinuria who are intolerant of ACE inhibitors.
Contraindicated in patients with bilateral renal artery stenosis.

**Calcium channel blockers**
There are important differences between calcium-channel blockers Dihydropyridine calcium-channel blockers are valuable in isolated systolic hypertension in the elderly when a low-dose thiazide is contra-indicated or not tolerated
‘Rate-limiting’ calcium-channel blockers (e.g. diltiazem, verapamil) may be valuable in angina; contra-indications include heart failure and heart block;
In recent large randomised trials, diltiazem and verapamil had no advantage over diuretics or beta-blockers in terms of overall cardiovascular prevention (less stroke and more MI with diltiazem, more heart failure with verapamil) or the total incidence of adverse effects.
Felodipine and long acting nifedipine formulations have been found to be as effective as diuretics or beta-blockers in the elderly in recent trials with limited statistical power; a difference in preventive efficacy cannot be ruled out.
In the ALLHAT trial, amlodipine had similar efficacy to thiazide diuretics, but was associated with an increased risk of heart failure based on clinical diagnosis.
Verapamil and diltiazem are contraindicated in patients with heart failure; long acting dihydropyridines may be used with caution.

**Other drugs**
A number of other drug classes, such as the centrally acting antihypertensives and the selective alpha-blockers, (a possible indication is prostatism; a contra-indication is urinary incontinence) are still used but there is no reliable evidence from randomised trials about their beneficial effect on cardiovascular risk.
Doxazosin (discontinued) was associated with an increased rate of congestive heart failure compared with chlorthalidone.

**Treatment regimens**
Major determinant of outcome is degree of BP control; this is more important than the drug groups used.
Start with a single antihypertensive agent at the lowest effective dose. Low dose thiazide diuretics are first line treatment in hypertension unless there is a contraindication or a specific indication for another drug.
Not all patients respond to all drugs; monitor response carefully.
Allow at least 4 weeks to gauge response to treatment, unless malignant or accelerated hypertension is present, or there are other indications for an urgent reduction in BP, e.g. dissecting aortic aneurysm. Single agents provide satisfactory control of BP in about 40–50% of people.
If response to the initial drug is inadequate after reaching the recommended dose, substitute or add another drug. Increasing the dose to the maximum may cause adverse effects without improving BP control. Use only 1 drug from any 1 class; avoid combining beta-blockers and verapamil because of the risk of severe bradycardia and heart block. Treatment should not be begun with combination products; reserve use for patients stabilised on similar doses of single ingredient products and who are not adequately controlled with a single agent. Diuretics should normally be one of the combinations.

**Resistant hypertension**

If BP remains above the target BP despite maximal doses of at least 2 appropriate agents, consider poor compliance, underlying secondary hypertension, intake of pro-hypertensive drugs or alcohol, presence of ‘white coat’ hypertension or measurement artefact, eg inadequate cuff size. Three or more different antihypertensives may be required in some patients.

**Special cases**

Elderly people: Systolic hypertension is common in elderly people and treatment benefits are well established. Low dose thiazide diuretics are highly beneficial in the elderly while beta-blockers are generally less effective.

Diabetes: Thiazide diuretics, ACE inhibitors and beta-blockers all reduce cardiovascular morbidity and mortality in people with both hypertension and diabetes.

In the ALLHAT trial, a thiazide diuretic (chlorthalidone) was shown to be at least as effective as an ACE inhibitor (lisinopril) in preventing cardiovascular morbidity in people with diabetes. ACE inhibitors may be preferred in patients with microalbuminuria or proteinuria as they have been shown to delay progression of renal disease.

In the UKPDS study in type 2 diabetes, the ACE inhibitor, captopril, and the beta-blocker, atenolol, seemed equally effective in reducing diabetes-related complications; people in the captopril arm had fewer adverse effects and better glycaemic control.

Losartan, an angiotensin II antagonist, reduced cardiovascular morbidity in a subgroup of patients with diabetes, hypertension and left ventricular hypertrophy. Data on preventive efficacy of dihydropyridines are conflicting. They may be used when first line treatments are not suitable.

**Hypertensive emergencies**

Aim to limit acute end organ damage. Rapid BP reduction (over several hours) is required in some circumstances (aortic dissection, severe pre-eclampsia). In other cases (malignant hypertension), gradual BP reduction over several days is sufficient and usually safer.

To reduce BP over several hours, consider IV sodium nitroprusside, glyceryl trinitrate or hydralazine.

For less urgent BP reduction, consider oral antihypertensive drugs, eg beta-blockers, ACE inhibitors, long acting dihydropyridines, clonidine. Diuretics are not usually suitable because of risk of hypovolaemia.

Magnesium sulfate reduces risk of eclampsia and maternal death in women with pre-eclampsia without any substantive harmful effect on mother and child.

**Treatment endpoints**

It should be noted that there is limited evidence from randomised clinical trials supporting target BP <140/90 mm Hg except in people with diabetes. In practice, BP can be lowered until side effects are unacceptable or until people prefer to stop adding or experimenting with additional drugs.

**Practice points**

- alcohol and some drugs, eg NSAIDs (including selective COX-2 inhibitors), sibutramine, corticosteroids, oral decongestants, MAOIs, venlafaxine and cyclosporin, may elevate BP
- consider and treat, as appropriate, other cardiovascular risk factors, eg by improving diabetic control, encouraging smoking cessation and considering lipid lowering therapy for those with a high absolute risk of cardiovascular disease
- low dose aspirin (75–150 mg daily) reduces risk of major cardiovascular events in treated hypertensive patients; increased risk of bleeding needs to be considered. Use of aspirin is recommended for secondary prevention and for primary prevention in high risk patients (see Antiplatelet drugs)
- several drugs are available as combination products; reserve use for patients stabilised on similar doses of single ingredient products

**02.05.01 Vasodilator anti-hypertensive drugs**
**NITROPRUSSIDE**

**Mode of action**
Diazoxide, hydralazine and minoxidil are predominantly arteriolar vasodilators with little effect on venous smooth muscle. Arteriolar vasodilation results in reflex sympathetic stimulation, leading to tachycardia and fluid retention. Beta-blockers and diuretics are often used with arteriolar vasodilators to compensate for reflex tachycardia and fluid retention. Sodium nitroprusside is a nonselective arteriolar and venous dilator.

**Indications**
Hypertensive emergency, Controlled hypotension during surgery to reduce bleeding, Acute heart failure

**Contraindications**
Compensatory hypertension (eg atroventricular shunt or coarctation of the aorta), vitamin B12 deficiency, cerebral or coronary artery disease, congenital (Leber's) optic atrophy, tobacco amblyopia, hypovolaemia, uncorrected anaemia

**Specific considerations**
Increased intracranial pressure, encephalopathy: risk of aggravation.
Hypothyroidism: thiocyanate (degradation product of sodium nitroprusside) inhibits both uptake and binding of iodine.
Hypothermia: risk of aggravation.
Pulmonary impairment: nitroprusside may worsen hypoxaemia.
Renal impairment: Reduced excretion of thiocyanate increases risk of toxicity; monitor thiocyanate concentrations during prolonged therapy.
Hepatic impairment: Avoid use in severe impairment.
Elderly: May require lower doses.
Pregnancy: Reserve for use in patients with hypertension not controlled by other agents; short term use for control of hypertensive crises may be safe provided that the pH and thiocyanate concentrations in maternal blood are monitored; ADEC category C.
Breastfeeding: not recommended if used >24 hours.

**Adverse effects**
Most often due to excessive hypotension or excessive cyanide accumulation; thiocyanate toxicity may also occur, especially with renal impairment.
Common: nausea, vomiting, sweating, apprehension, headache, restlessness, muscle twitching, retrosternal discomfort, palpitations, dizziness, abdominal pain (with too rapid reduction in BP)
Infrequent: postural hypotension, hypothyroidism, paraesthesia, feeling of warmth, rash, flushing, increased intracranial pressure
Rare: thrombocytopenia, methaemoglobinemia, phlebitis
Toxicity: Toxicity may occur, particularly with prolonged infusion or higher than recommended maximum dose, due to accumulation of thiocyanate or cyanide. In normal renal function cyanide accumulates with infusion rate of >2 micrograms/kg/minute. Risk of toxicity is greater in renal impairment because of reduced excretion of thiocyanate. Thiocyanate toxicity causes confusion, psychosis, tinnitus, blurred vision, nausea, dyspnoea, hypothyroidism and ataxia.
Cyanide toxicity causes tachycardia, sweating, hyperventilation, headache, arrhythmias, metabolic acidosis, areflexia, coma, hypotension, pink colour of skin and mucous membranes, shallow breathing, dilated pupils and death.

**Dosage**
*Give by IV infusion*
Hypertensive emergency: Initially, 0.3 microgram/kg/minute, increase every few minutes until desired effect is achieved. Maintenance, 0.5–6 micrograms/kg/minute (20–400 micrograms/minute). Maximum, 10 micrograms/kg/minute.
Controlled hypotension during surgery: Maximum, 1.5 micrograms/kg/minute.

**Administration instructions**
Dilute with glucose 5%; do not administer by direct injection.
Infusion solution should be protected from light, eg with aluminium foil.
Final infusion concentration should be 50–100 micrograms/mL (ie 50 mg of sodium nitroprusside in 500–1000 mL glucose 5%).

**Practice points**
• monitor intra-arterial BP continuously during infusion and titrate infusion rate carefully to avoid excessive hypotension
• abrupt withdrawal of sodium nitroprusside may cause rebound hypertension; withdraw over at least 10–30 minutes to avoid rebound
• usual duration of treatment should not exceed 72 hours because of cumulative thiocyanate toxicity and the possibility of cyanide toxicity; monitor thiocyanate concentrations

Products
NITROPRUSIDE AMPS 60 MG/AMP IV 10 ML AMP (NIPRUSS®)

02.05.02 Centrally acting anti-hypertensives

METHYLDOPA
Indications
Hypertension
Contraindications
Active hepatic disease, phaeochromocytoma
Specific considerations
Depression: may be exacerbated by methyldopa.
Renal impairment: May respond to lower dosage; start treatment with usual initial dosage, increased dosage may not be required.
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Safe to use.
Adverse effects
Common: sedation, dizziness, light-headedness, tiredness, weakness, dry mouth, fever, headache, nausea, diarrhoea, positive direct Coombs’ test
Infrequent: haemolytic anaemia, eosinophilia, orthostatic hypotension, bradycardia, oedema, constipation, sore tongue, depression, rash, nasal congestion, sleep disturbance, impotence
Rare: hepatotoxicity with acute or chronic active hepatitis or hepatic necrosis, leucopenia, thrombocytopenia, pancreatitis, reduced libido, hyperprolactinaemia (causing galactorrhoea in women and gynaecomastia in men)
Dosage
Adult: Initially 125–250 mg twice daily for 2 days, then adjust by 250–500 mg daily at 2-day intervals. Maintenance, 125–500 mg 2–4 times daily. When used with other antihypertensives daily dose is usually 500 mg or less.
Patient counselling
This medicine may make you feel drowsy or light-headed especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
You may feel dizzy on standing when you first start taking this medicine or when the dose is increased. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy..
Practice points
• the sedating effect of methyldopa is exacerbated by dose increases; increase dosage at night to minimise inconvenience of increased sedation
• monitor blood count and liver function during first 6–12 weeks of treatment
Products
METHYL DOPA TABS 250 MG (DOPANORE®, MEDORAM®)

MOXONIDINE
Indications
Mild to moderate essential hypertension
Cautions
Renal impairment; avoid abrupt withdrawal (if concomitant treatment with beta-blocker has to be stopped, discontinue beta-blocker first, then moxonidine after few days); interactions.
Contra-indications
History of angioedema; conduction disorders (sick sinus syndrome, sino-atrial block, second- or third-degree AV block); bradycardia; life-threatening arrhythmia; severe heart failure; severe coronary artery disease, unstable angina; severe liver disease or severe renal impairment; also on theoretical grounds: Raynaud’s syndrome, intermittent claudication, epilepsy, depression, Parkinson’s disease, glaucoma; pregnancy (Appendix 4); breast-feeding
Side-effects
Dry mouth; headache, fatigue, dizziness, nausea, sleep disturbance (rarely sedation), asthenia, vasodilatation; rarely skin reactions

Dose
200 micrograms once daily in the morning, increased if necessary after 3 weeks to 400 micrograms daily in 1–2 divided doses; max. 600 micrograms daily in 2 divided doses (max. single dose 400 micrograms)

Products
MOXONIDINE TABS 0.4 MG (PHYSIOTENS®)

CLOPAMIDE + DIHYDROERGOCRISTINE + RESERPINE

CLOPAMIDE
Is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide even though it does not contain a thiazide ring system. It is used for oedema, including that associated with heart failure, and for hypertension.

Diuresis starts in 1 to 2 hours, reaches a maximum in about 3 to 6 hours, and lasts for up to 24 hours. In the treatment of oedema the usual dose is 10 to 40 mg daily by mouth; frequency may be reduced for maintenance. For hypertension doses of 5 to 10 mg daily, either alone, or with other antihypertensives have been used.

Dihydroergocristine Mesilate
Dihydroergocristine mesilate is a component of co-dergocrine mesilate and has similar actions. In some countries it has been given by mouth in the symptomatic treatment of mental deterioration associated with cerebrovascular insufficiency and in peripheral vascular disease. It has also been given by intramuscular injection.

RESERPINE

Adverse Effects
Adverse effects commonly include nasal congestion, headache and CNS symptoms including depression, drowsiness, dizziness, lethargy, nightmares, and symptoms of increased gastrointestinal tract motility including diarrhoea, abdominal cramps, and, at higher doses, increased gastric acid secretion. Respiratory distress, cyanosis, anorexia, and lethargy may occur in infants whose mothers have received reserpine prior to delivery. Higher doses may cause flushing, bradycardia, severe depression which may lead to suicide, and extrapyramidal effects. Hypotension, coma, convulsions, respiratory depression and hypothermia also occur in overdosage. Hypotension is also more common in patients following a cerebrovascular accident.

Breast engorgement and galactorrhoea, gynaecomastia, increased prolactin concentrations, decreased libido, impotence, sodium retention, oedema, decreased or increased appetite, weight gain, mirosis, dry mouth, slialorrhoea, dysuria, rashes, pruritus, and thrombocytopenic purpura have also been reported.

Reserpine has been shown to be tumorigenic in rodents following administration of large doses. Several reports have suggested an association between the ingestion of reserpine and the development of neoplasms of the breast but other surveys have failed to confirm the association.

Precautions
Reserpine should not be used in patients with depression or a history of depression, with active peptic ulcer disease or ulcerative colitis, or in patients with Parkinson's disease. It should also be avoided in phaeochromocytoma. It should be used with caution in debilitated or elderly patients, and in the presence of cardiac arrhythmias, myocardial infarction, renal insufficiency, gallstones, epilepsy, or allergic conditions such as bronchial asthma. Reserpine is contra-indicated in patients receiving ECT; if ECT is required in patients who have been taking reserpine an interval of at least 7 to 14 days should be allowed to elapse between the last dose of reserpine and the commencement of the shock treatment.

Interactions
Patients taking reserpine may be hypersensitive to adrenaline and other direct-acting sympathomimetics which should not be given except to antagonise reserpine. The effects of indirect-acting sympathomimetics such as ephedrine may be decreased by reserpine. The hypotensive effects of reserpine are enhanced by thiazide diuretics and other antihypertensives. Reserpine may cause excitation and hypertension in patients receiving MAOIs. Concurrent administration of digitalis or quinidine may cause cardiac arrhythmias. Reserpine may enhance the effects of CNS depressants.

Uses and Administration
Reserpine is an alkaloid obtained from the roots of certain species of Rauwolfia (Apocynaceae), mainly Rauwolfia serpentina and R. vomitoria, or by synthesis. The material obtained from natural sources may contain closely related alkaloids.
Reserpine is an antihypertensive drug that causes depletion of noradrenaline stores in peripheral sympathetic nerve terminals and depletion of catecholamine and serotonin stores in the brain, heart, and many other organs resulting in a reduction in blood pressure, bradycardia, and CNS depression. The hypotensive effect is mainly due to a reduction in cardiac output and a reduction in peripheral resistance. Cardiovascular reflexes are partially inhibited, but orthostatic hypotension is rarely a problem at the doses used in hypertension. When given by mouth the full effect is only reached after several weeks of continued treatment and persists for up to 6 weeks after treatment is discontinued. Reserpine has been used in the management of hypertension and in chronic psychoses such as schizophrenia. It has also been tried in the treatment of Raynaud’s syndrome.

In hypertension, reserpine may be given by mouth in an initial dose of up to 500 micrograms daily for about 2 weeks, subsequently reduced to the lowest dose necessary to maintain the response; some sources recommend an initial dose of 50 to 100 micrograms. A maintenance dose of about 100 to 250 micrograms daily may be adequate and 500 micrograms should not normally be exceeded. To reduce side-effects and tolerance smaller doses of reserpine may be used with a thiazide diuretic.

**Products**

CLOPAMIDE 5 MG+DIHYDROERGOCRISTINE MESILATE 0.5 MG+RESERPINE 0.1 MG TABS

(BRINERDIN®)

**02.05.03 Drugs affecting Renin Angiotensin system**

**02.05.03.01 Angiotensin-converting enzyme Inhibitors (ACE Inhibitors)**

**ACE INHIBITORS**

**Mode of action**

ACE inhibitors block conversion of angiotensin I to angiotensin II and also inhibit the breakdown of bradykinin. They reduce the effects of angiotensin II-induced vasoconstriction, sodium retention and aldosterone release. They also reduce the effect of angiotensin on sympathetic nervous activity and as a growth factor.

**Indications**

Hypertension, Heart failure, Diabetic nephropathy (type 1 diabetes), Prevention of progressive renal failure in patients with persistent proteinuria (>1 g/day), Asymptomatic left ventricular dysfunction, Post MI (acute treatment or in patients with left ventricular dysfunction or heart failure), Reduction of risk of cardiovascular events in specific patients

**Contraindications**

Angioedema, Renal artery stenosis (bilateral, or unilateral with a solitary kidney)

**Specific considerations**

Hypovolaemia, dehydration (eg taking a diuretic): increases risk of first dose hypotension.

Aortic or mitral valve stenosis, cardiac outflow tract obstruction: risk of excessive hypotension, use with caution.

Haemodialysis with high flux polyacrylonitrile membranes (AN 69): may result in anaphylactoid reactions; similar reactions may occur in patients on low density lipoprotein apheresis with dextran sulfate.

Treatment with drugs which can increase potassium concentration, eg cyclosporin: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.

Renal impairment: Increases risk of hyperkalaemia; may further impair renal function, especially in people with hypovolaemia, renal artery stenosis, or if used with NSAIDs (including selective COX-2 inhibitors).

Renal impairment may affect the excretion of most ACE inhibitors; dosage adjustment may be necessary.

Myelosuppressive effect in endstage renal failure; may require increased epoetin dosage.

Surgery: Excessive hypotension may occur during anaesthesia and after surgery.

Elderly: May be more predisposed to first dose hypotension and hyperkalaemia than younger patients. Start treatment with lower doses.

Pregnancy: Avoid use; use in second and third trimester may cause a range of abnormalities including renal dysfunction and oligohydramnios, which can be associated with fetal death in utero; there is insufficient information to determine conclusively that ACE inhibitors are safe in the first trimester; pregnant women taking ACE inhibitors should be changed as quickly as possible to an alternative antihypertensive; ADEC category D.

Breastfeeding: No adverse effects in infant reported with captopril or enalapril; insufficient information to confirm safety of other ACE inhibitors.

Women: Women of child-bearing age should use adequate contraception.

**Adverse effects**

Common: hypotension, cough, hyperkalaemia, headache, dizziness, fatigue, nausea, renal impairment
Infrequent: anaphylactoid reactions, angioedema (early or delayed onset), rash, itching, palpitations, chest pain, flushing, fever, taste disturbances, vomiting, anorexia, diarrhoea, constipation, stomatitis, dry mouth, sore throat, hoarseness, muscle cramps, elevated hepatic transaminases and bilirubin, abnormal dreams
Rare: hepatitis (cholestatic or hepatocellular), pancreatitis, proteinuria, thrombocytopenia, neutropenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, eosinophilia, myalgia, arthralgia, neuropathy, paraesthesia, photosensitivity, psoriasis, pemphigus and toxic epidermal necrolysis, gynaecomastia, visceral angioedema

Comparative information
Advantages for specific ACE inhibitors are claimed based on pharmacokinetic, metabolic or tissue ACE-binding characteristics; however, these do not translate into significant clinical differences.
Hypertension: All ACE inhibitors have similar antihypertensive efficacy; adverse effects are usually class effects and do not differ significantly between agents.
Most (except captopril) maintain an antihypertensive effect for up to 24 hours and can be given once daily.
Fosinopril, enalapril, quinapril and perindopril are available either alone or as combination products with a thiazide diuretic (hydrochlorothiazide or indapamide). Reserve use for patients who are stabilised on similar doses of single ingredient products.
Heart failure: Most ACE inhibitors are marketed for treatment of heart failure; they improve symptoms, reduce mortality and risk of hospitalisation.
Post MI: Captopril, ramipril and trandolapril reduce mortality and prevent development of heart failure post MI in patients with left ventricular dysfunction or heart failure; lisinopril is indicated for MI within 24 hours of onset in patients who are haemodynamically stable, with or without left ventricular dysfunction; enalapril is marketed for asymptomatic left ventricular dysfunction; patients with lower ejection fraction seem to derive greater benefit from ACE inhibitors.

Prevention of cardiovascular events
Ramipril reduces risk of MI, stroke, cardiovascular death or need for revascularisation procedures in patients >55 years with coronary artery disease, stroke or peripheral vascular disease; and in diabetic patients >55 years with one or more risk factors (hypertension, smoking, microalbuminuria, high total cholesterol, low HDL cholesterol, previous vascular disease).

Proteinuria
ACE inhibitors reduce progression to macroalbuminuria in normotensive diabetic patients with microalbuminuria. Captopril is indicated for diabetic nephropathy in type 1 diabetes; ramipril is indicated for persistent proteinuria in diabetic or non-diabetic nephropathy.

Patient counselling
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.
Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

Practice points
- when initiating ACE inhibitors:
  o stop potassium supplements and potassium-sparing diuretics
  o stop other diuretics for 24 hours
  o start with a low dose
- check renal function and electrolytes before starting ACE inhibitor and review after 1–2 weeks

CAPTOPRIL
Mode of action
Angiotensin converting enzyme (ACE) inhibitors block conversion of angiotensin I to angiotensin II and also inhibit the breakdown of bradykinin. They reduce the effects of angiotensin II-induced vasoconstriction, sodium retention and aldosterone release. They also reduce the effect of angiotensin on sympathetic nervous activity and as a growth factor.

Indications
Hypertension, Heart failure, Post MI in patients with left ventricular dysfunction, Diabetic nephropathy (type 1 diabetes), Prevention of progressive renal failure in patients with persistent proteinuria (>1 g/day), Asymptomatic left ventricular dysfunction, Reduction of risk of cardiovascular events in specific patients

Contraindications
Angioedema, Renal artery stenosis (bilateral, or unilateral with a solitary kidney)

Specific considerations
Collagen vascular disorders (eg scleroderma, systemic lupus erythematosus), severe renal impairment: may predispose to neutropenia or agranulocytosis.

- Hypovolaemia, dehydration (eg during diuretic treatment): increases risk of first dose hypotension. Aortic or mitral valve stenosis, cardiac outflow tract obstruction: risk of excessive hypotension, use with caution.
- Haemodialysis with high flux polyacrylonitrile membranes (AN 69): may result in anaphylactoid reactions; similar reactions may occur in patients on low density lipoprotein apheresis with dextran sulfate.
- Treatment with drugs which can increase potassium concentration, eg cyclosporin: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.
- Renal impairment: Increases risk of hyperkalaemia; may further impair renal function, especially in people with renal artery stenosis, hypovolaemia, or if used with NSAIDs (including selective COX-2 inhibitors).

Renal impairment may affect the excretion of most ACE inhibitors; dosage adjustment may be necessary.

Myelosuppressive effect in endstage renal failure; may require increased epoetin dosage.

Surgery: Excessive hypotension may occur during anaesthesia and after surgery.

Elderly: May be more predisposed to first dose hypotension and hyperkalaemia than younger patients. Start treatment with lower doses in the elderly.

Pregnancy: Avoid use; use in second and third trimester may cause a range of abnormalities including renal dysfunction and oligohydramnios, which can be associated with fetal death in utero; there is insufficient information to determine conclusively that ACE inhibitors are safe in the first trimester; pregnant women taking ACE inhibitors should be changed as quickly as possible to an alternative antihypertensive; ADEC category D.

Breastfeeding: No adverse effects in infant reported; insufficient information to confirm safety of other ACE inhibitors.

**Adverse effects**

Common: hypotension, cough, hyperkalaemia, headache, dizziness, fatigue, nausea, renal impairment

Infrequent: anaphylactoid reactions, angioedema (early or delayed onset), rash, itching, palpitations, chest pain, flushing, fever, taste disturbances, vomiting, anorexia, diarrhoea, constipation, stomatitis, dry mouth, sore throat, hoarseness, muscle cramps, elevated hepatic transaminases and bilirubin, abnormal dreams

Rare: hepatitis (cholestatic or hepatocellular), pancreatitis, proteinuria, thrombocytopenia, neutropenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, eosinophilia, myalgia, arthralgia, neuropathy, paraesthesia, psoriasis, photosensitivity, pemphigus and toxic epidermal necrolysis, gynaecomastia, visceral angioedema

**Dosage**

- Hypertension, Initially 12.5 mg twice daily, increased at intervals of 2–4 weeks to 25–50 mg twice daily.
- Heart failure, Initially 6.25 mg 3 times daily, increased at 2-week intervals to 25–75 mg twice daily. Maximum 150 mg daily.
- Myocardial infarction, Initiate treatment in stable patients 3 days post MI at 6.25 mg 3 times daily; increase up to 25 mg 3 times daily over several days to final target dose of 50 mg 3 times daily.
- Diabetic nephropathy, 25 mg 3 times daily.
- Renal impairment, elderly, or concurrent diuretic treatment, Initially 6.25 mg twice daily.

**Administration instructions**

Oral solution is intended for dose titration; mix with a drink such as water, fruit juice, tea, coffee or cola, and take immediately after adding captopril.

**Patient counselling**

This medicine is absorbed best if taken 1 hour before food.

You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.

Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

**Practice points**

when initiating ACE inhibitors:
- stop potassium supplements and potassium-sparing diuretics
- stop other diuretics for 24 hours
- start with a low dose

- check renal function and electrolytes before starting ACE inhibitor and review after 1–2 weeks
- onset of ACE inhibitor associated angioedema may not occur for several years
ENALAPRIL
Mode of action
Same as Captopril
Indications
Hypertension (includes combination with hydrochlorothiazide)
Heart failure
Asymptomatic left ventricular dysfunction
Contraindications
Angioedema: Renal artery stenosis (bilateral, or unilateral with a solitary kidney)
Specific considerations
Adverse effects
Same as Captopril
Dosage
Hypertension: Initially 5 mg daily, increased at intervals of 1–2 weeks up to 10–40 mg daily as 1 or 2 doses.
Heart failure: Initially 2.5 mg daily, increased up to 10–20 mg daily as 1 or 2 doses.
Left ventricular dysfunction: Initially 2.5 mg daily, increased up to 20 mg daily in 2 doses.
Patient counselling
Same as Captopril
Renal impairment, elderly, concurrent diuretic treatment: Initially 2.5 mg daily.
Products
ENALAPRIL TABS 5 MG (AS MALEATE) (ACE PRESS®, ANGIOTEC®, ENACARD®, LAPRIL®, RENITEC®)
ENALAPRIL TABS 10 MG (AS MALEATE) (ACE PRESS®, ANGIOTEC®, ENACARD®, LAPRIL®, VASOPRIL®)
ENALAPRIL TABS 20 MG (AS MALEATE) (ACE PRESS®, ANGIOTEC®, ENACARD®, LAPRIL®, RENITEC®, VASOPRIL®, UTLCADEX®)

FOSINOPRIL
Mode of action
Same as Captopril
Indications
Same as Captopril
Contraindications
Angioedema: Renal artery stenosis (bilateral, or unilateral with a solitary kidney)
Specific considerations
Adverse effects
Same as Captopril
Dosage
Hypertension: Initially 10 mg once daily, increased up to 40 mg once daily.
Heart failure: Initially 5–10 mg once daily, increased up to 10–40 mg once daily.
Renal impairment, elderly, concurrent diuretic treatment, Initially 5–10 mg daily.
Patient counselling
Same as Captopril
Practice points: same as Captopril
Products
FOSINOPRIL TABS 20 MG (STARIL®)

LISINOPRIL
Mode of action
same as Captopril.
Indications
same as Captopril
Contraindications
same as Captopril
Specific considerations
Same as Captopril
Adverse effects
Same as Captopril
Dosage
Hypertension: Initially 5–10 mg daily, increased at intervals of 2–4 weeks up to 20 mg once daily if necessary. Maximum 40 mg daily.
Heart failure: Initially 2.5 mg daily, increased at 4-week intervals up to 20 mg daily according to clinical response.
Myocardial infarction: Initially 5 mg within 24 hours of the onset of symptoms (2.5 mg in patients with systolic BP <120 mm Hg), followed by 5 mg after 24 hours; then 10 mg once daily for 6 weeks; continue treatment in patients developing heart failure.
Renal impairment, elderly, concurrent diuretic treatment: Initially 2.5–5 mg daily.

Patient counselling
Same as Captopril
Practice points: same as Captopril

Products
LISINOPRIL TABS 5 MG (INOPRIL®, LINOPRIL®, LISOCARD®, LISOPRIL®, ZENORIL®, ZESTRIL®)
LISINOPRIL TABS 20 MG (INOPRIL®, LINOPRIL®, LISOCARD®, LISOPRIL®, ZENORIL®, ZESTRIL®)

PERINDOPRIL
Mode of action
Same as Captopril
Indications
Hypertension (includes combination with indapamide)
Heart failure
Reduction of risk of MI or cardiac arrest in people with established heart disease without heart failure
Contraindications
Angioedema: Renal artery stenosis (bilateral, or unilateral with a solitary kidney)
Specific considerations
Same as Captopril
Adverse effects
Same as Captopril
Dosage
Hypertension
Initially 4 mg once daily. Maximum 8 mg daily.
Renal impairment
Initial dose according to creatinine clearance:
- 30–60 mL/minute, 2 mg once daily
- 15–30 mL/minute, 2 mg on alternate days
- <15 mL/minute, 2 mg on day of dialysis.
Elderly or at risk of ACE inhibitor-induced hypotension
Initially 2 mg once daily.
Combination with indapamide: For additional information see Indapamide
Reserve use for patients stabilised on similar doses of each drug. 1 tablet once daily.
Heart failure: Initially 2 mg once daily; increase up to 4 mg once daily.
Reduction of risk of cardiovascular events: Initially 4 mg once daily for 2 weeks; increase up to 8 mg daily depending on tolerance and renal function.
Elderly: Initially 2 mg once daily for 1 week, then 4 mg once daily the next week; increase up to 8 mg daily depending on tolerance and renal function.

**Patient counselling**
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.
Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

**Practice points**
when initiating ACE inhibitors:
- stop potassium supplements and potassium-sparing diuretics
- stop other diuretics for 24 hours
- start with a low dose
- check renal function and electrolytes before starting ACE inhibitor and review after 1–2 weeks
- onset of ACE inhibitor associated angioedema may not occur for several years

**Products**
PERINDOPRIL TABS 2 MG (COVERSYL®)
PERINDOPRIL TABS 4 MG (COVERSYL®)

**RAMIPRIL**

**Mode of action**
Same as Captopril

**Indications**
Hypertension
Post MI in patients with heart failure
Prevention of MI, stroke, cardiovascular death or need for revascularisation procedures in patients >55 years with:
- coronary artery disease, stroke or peripheral vascular disease, or
- diabetes and 1 or more risk factors (hypertension, smoking, microalbuminuria, high total cholesterol, low HDL cholesterol, previous vascular disease)
Prevention of progressive renal failure in patients with persistent proteinuria (>1 g/day)

**Contraindications**
Angioedema: Renal artery stenosis (bilateral, or unilateral with a solitary kidney)

**Specific considerations**
Same as Captopril

**Adverse effects**
Same as Captopril

**Dosage**
Hypertension: 2.5 mg once daily, increase after 2–3 weeks to 5 mg if necessary. Maximum 10 mg daily, in 1 or 2 doses.
Heart failure: Initially 2.5 mg twice daily, beginning 2–10 days after MI in patients who are haemodynamically stable; increase at intervals of 1–3 days to 5–10 mg daily in 2 divided doses.
Increased cardiovascular risk
Initially 2.5 mg once daily, increase after 1 week to 5 mg once daily and after 3 weeks to 10 mg once daily.
Renal impairment, elderly, concurrent diuretic treatment: Initially 1.25 mg once daily.
Proteinuria: Initially 1.25 mg once daily, double at intervals of 2–3 weeks, depending on tolerance, up to 5 mg once daily.

**Patient counselling**
Same as Captopril

**Practice points**
Same as Captopril

**Products**
RAMIPRIL TABS 5 MG (TRITACE®)

02.050.3.02 Angiotensin-II receptor Antagonists
Also known as sartans.

Mode of action
Competitively block binding of angiotensin II to type 1 angiotensin (AT₁) receptors blocking effects of angiotensin more selectively than ACE inhibitors. They reduce angiotensin-induced vasoconstriction, sodium reabsorption and aldosterone release.

Indications
Marketed: Hypertension, Reduction in progression of renal disease in patients with type 2 diabetes, hypertension and microalbuminuria (irbesartan) or proteinuria (irbesartan, losartan)
Accepted: Heart failure in patients unable to tolerate ACE inhibitors

Contraindications
Hypersensitivity reactions, eg urticaria, Angioedema, Renal artery stenosis (bilateral, or unilateral with solitary kidney).

Specific considerations
Volume or sodium depletion: excessive hypotension may occur.
Aortic or mitral valve stenosis, cardiac outflow tract obstruction: risk of excessive hypotension, use with caution.
Primary hyperaldosteronism: antihypertensive effect may be reduced.
Treatment with drugs which can increase potassium concentration, eg cyclosporin: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.
Renal impairment: Renal function may worsen; increases risk of hyperkalaemia. Use lower initial doses and monitor potassium.
Pregnancy: Avoid use; drugs acting directly on the renin–angiotensin system can injure, and may be fatal to, the developing fetus. There is insufficient information to determine conclusively that these drugs are safe in the first trimester; pregnant women taking them should be changed as quickly as possible to an alternative antihypertensive; ADEC category D.
Breastfeeding: No data available; avoid use.
Women: Women of child-bearing age should use adequate contraception.

Adverse effects
Common: dizziness, headache, hyperkalaemia
Infrequent: first dose orthostatic hypotension, rash, diarrhoea, dyspepsia, abnormal liver function, muscle cramp, myalgia, back pain, insomnia, decreased haemoglobin, renal impairment, pharyngitis, nasal congestion
Rare: cough, urticaria, angioedema, Henoch-Schönlein purpura, hepatitis, taste disturbance, migraine

Comparative information
Hypertension
Angiotensin II antagonists lower BP to a similar extent to other major antihypertensive drug classes (eg beta-blockers, ACE inhibitors).
Losartan reduces cardiovascular morbidity and mortality more than atenolol in patients with both hypertension and left ventricular hypertrophy, especially in patients with diabetes.
Both losartan and irbesartan are marketed to reduce the progression of renal disease in patients who have type 2 diabetes, hypertension and proteinuria (or microalbuminuria for irbesartan).
Candesartan, eprosartan, irbesartan and telmisartan are available either alone or as combination products with a thiazide diuretic (hydrochlorothiazide). Reserve use for patients who are not adequately controlled with a single agent and are stabilised on similar doses of single ingredient products.

Heart failure
Candesartan improves prognosis in heart failure and is a suitable alternative to ACE inhibitors in patients unable to tolerate them. Angiotensin II antagonists may further decrease cardiovascular morbidity and mortality when added to an ACE inhibitor in patients with low left ventricular ejection fraction but may also increase risk of adverse effects. The combination is best reserved for specialist management at this stage.

Patient counselling
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.
Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

Practice points
- before starting angiotensin II antagonists stop potassium supplements and potassium-sparing diuretics; check renal function and electrolytes and review regularly.
- unlike ACE inhibitors, angiotensin II antagonists do not inhibit the breakdown of bradykinin and may be useful if unable to tolerate an ACE inhibitor because they:
  - cause less cough than ACE inhibitors
  - may be used if there is a history of angioedema caused by an ACE inhibitor (with close monitoring; as there is a small risk of recurrence)
- may be used with low dose thiazide diuretics for additive antihypertensive effect if response to angiotensin II antagonist alone is inadequate.
- maximum antihypertensive effect occurs about 4–6 weeks after starting treatment.

**Candesartan**

**Mode of action**
Competitively block the binding of angiotensin II to type 1 angiotensin (AT1) receptors and therefore block the effects of angiotensin more selectively than do the ACE inhibitors; reduce angiotensin-induced vasoconstriction, sodium reabsorption and aldosterone release.

**Indications**
Marketed: Hypertension (includes combination with hydrochlorothiazide), Reduction in progression of renal disease in patients with type 2 diabetes, Heart failure in patients unable to tolerate ACE inhibitors or in combination with ACE inhibitors in patients with low left ventricular ejection fraction
Accepted: Heart failure with impaired left ventricular systolic function in patients unable to tolerate ACE inhibitors

**Contraindications**
Hypersensitivity reactions, eg urticaria, angioedema, Renal artery stenosis (bilateral, or unilateral with solitary kidney)

**Specific considerations**
Volume or sodium depletion: excessive hypotension may occur.
Aortic or mitral valve stenosis, cardiac outflow tract obstruction: risk of excessive hypotension, use with caution.
Primary hyperaldosteronism: antihypertensive effect may be reduced.
*Treatment with drugs which can increase potassium concentration, eg cyclosporin*: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.
Renal impairment: Renal function may worsen; increases risk of hyperkalaemia. Use lower initial doses and monitor potassium.
Pregnancy: Avoid use; drugs acting directly on the renin–angiotensin system can injure, and may be fatal to, the developing fetus. There is insufficient information to determine conclusively that these drugs are safe in the first trimester; pregnant women taking them should be changed as quickly as possible to an alternative antihypertensive; ADEC category D.
Breastfeeding: No data available; avoid use.
Women: Women of child-bearing age should use adequate contraception.

**Adverse effects**
Common: dizziness, headache, hyperkalaemia
Infrequent: first dose orthostatic hypotension, rash, diarrhoea, dyspepsia, muscle cramp, myalgia, back pain, insomnia, nasal congestion, abnormal liver function, decreased haemoglobin, renal impairment, pharyngitis
Rare: cough, urticaria, angioedema, Henoch-Schönlein purpura, hepatitis, taste disturbance, migraine

**Dosage:**
Hypertension: Usually 8 mg once daily; increase if necessary to 16 mg once daily.
Combination with hydrochlorothiazide
For additional information see Hydrochlorothiazide
Reserve use for patients stabilised on similar doses of each drug. 1 tablet once daily.
Heart failure: Start at 4 mg once daily; double the dose at intervals of at least 2 weeks to highest tolerated dose (maximum 32 mg daily).
Severe renal impairment: Start at 4 mg once daily; may require lower maximum dose.

**Patient counselling**
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.
Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

**Practice points**
• before starting angiotensin II antagonists stop potassium supplements and potassium-sparing diuretics; check renal function and electrolytes and review regularly
• unlike ACE inhibitors, angiotensin II antagonists do not inhibit the breakdown of bradykinin and may be useful if unable to tolerate an ACE inhibitor because they:
  o cause less cough than ACE inhibitors
  o may be used if there is a history of angioedema caused by an ACE inhibitor (with close monitoring as there is a small risk of recurrence)
• may be used with low dose thiazide diuretics for additive antihypertensive effect if response to angiotensin II antagonist alone is inadequate
• maximum antihypertensive effect occurs about 4–6 weeks after starting treatment

Products
Candesartan Tabs 8 mg (As Cilexetil) (Atacand®, Blopres®)
Candesartan Tabs 16 mg (As Cilexetil) (Atacand®, Blopres®)

Eprosartan

Mode of action
Same as Candesartan.

Indications
Marketed: Hypertension
Reduction in progression of renal disease in patients with type 2 diabetes
Accepted: Heart failure in patients unable to tolerate ACE inhibitors

Contraindications
Hypersensitivity reactions, eg urticaria, Angioedema. Renal artery stenosis (bilateral, or unilateral with solitary kidney)

Specific considerations
Volume or sodium depletion: excessive hypotension may occur.
Aortic or mitral valve stenosis, cardiac outflow tract obstruction: risk of excessive hypotension, use with caution.
Primary hyperaldosteronism: antihypertensive effect may be reduced.
Treatment with drugs which can increase potassium concentration, eg cyclosporin: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.
Renal impairment: Renal function may worsen; increases risk of hyperkalaemia. Use lower initial doses and monitor potassium.
Hepatic impairment: Lower dosage is required.
Pregnancy: Avoid use; drugs acting directly on the renin–angiotensin system can injure, and may be fatal to, the developing fetus. There is insufficient information to determine conclusively that these drugs are safe in the first trimester; pregnant women taking them should be changed as quickly as possible to an alternative antihypertensive; ADEC category D.
Breastfeeding: No data available; avoid use.

Adverse effects
Common: dizziness, headache, hyperkalaemia
Infrequent: first dose orthostatic hypotension, rash, diarrhoea, dyspepsia, muscle cramp, myalgia, back pain, insomnia, nasal congestion, abnormal liver function, decreased haemoglobin, renal impairment, pharyngitis
Rare: cough, urticaria, angioedema, Henoch–Schönlein purpura, hepatitis, taste disturbance, migraine

Dosage
Initially 600 mg once daily; increase if necessary to 800 mg once daily. Start at 400 mg once daily if taking diuretics, elderly, or with hepatic or renal impairment.

Patient counselling
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.
Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

Practice points
before starting angiotensin II antagonists stop potassium supplements and potassium-sparing diuretics; check renal function and electrolytes and review regularly
• unlike ACE inhibitors, angiotensin II antagonists do not inhibit the breakdown of bradykinin and may be useful if unable to tolerate an ACE inhibitor because they:
  o cause less cough than ACE inhibitors
may be used if there is a history of angioedema caused by an ACE inhibitor (with close monitoring as there is a small risk of recurrence)

- may be used with low dose thiazide diuretics for additive antihypertensive effect if response to angiotensin II antagonist alone is inadequate
- maximum antihypertensive effect occurs about 4–6 weeks after starting treatment

**Products**

**EPROSARTAN CAPS 600 MG (AS MESILATE) (TEVETEN®)**

**LOSARTAN**

**Mode of action**
Same as Candesartan

**Indications**
Marketed: Hypertension, Reduction in progression of renal disease in patients with type 2 diabetes, hypertension and proteinuria (urinary albumin to creatinine ratio greater than or equal to 300 mg/g or proteinuria >500 mg/24 hours)
Accepted: Heart failure in patients unable to tolerate ACE inhibitors

**Contraindications**
Hypersensitivity reactions, e.g. urticaria, angioedema,
Renal artery stenosis (bilateral, or unilateral with solitary kidney)

**Specific considerations**
Hepatic impairment: Lower dosage may be required.
Volume or sodium depletion: excessive hypotension may occur.
Aortic or mitral valve stenosis, cardiac outflow tract obstruction: risk of excessive hypotension, use with caution.
Primary hyperaldosteronism: antihypertensive effect may be reduced.
Treatment with drugs which can increase potassium concentration, e.g. cyclosporin: increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.
Renal impairment: Renal function may worsen; increases risk of hyperkalaemia. Use lower initial doses and monitor potassium.

Pregnancy: Avoid use; drugs acting directly on the renin–angiotensin system can injure, and may be fatal to, the developing fetus. There is insufficient information to determine conclusively that these drugs are safe in the first trimester; pregnant women taking them should be changed as quickly as possible to an alternative antihypertensive; ADEC category D.

Breastfeeding: No data available; avoid use.

**Adverse effects**
Common: dizziness, headache, hyperkalaemia
Infrequent: first dose orthostatic hypotension, rash, diarrhoea, dyspepsia, muscle cramp, myalgia, back pain, insomnia, nasal congestion, abnormal liver function, decreased haemoglobin, renal impairment, pharyngitis
Rare: cough, urticaria, angioedema, Henoch-Schönlein purpura, hepatitis, taste disturbance, migraine

**Dosage**
Usually 50 mg once daily; increase if necessary after 3–6 weeks to 100 mg once daily. Start at 25 mg once daily in people taking diuretics

**Patient counselling**
Same as Candesartan

**Practice points**
Same as Candesartan

**Products**

**LOSARTAN TABS 50 MG (AS POTASSIUM) (AZARTEN®, COZAAR®, LACINE®, LOWZAN®)**

**TELMISARTAN**

**Mode of action**
Same as Candesartan

**Indications**
Marketed: Hypertension, Reduction in progression of renal disease in patients with type 2 diabetes, hypertension and proteinuria (urinary albumin to creatinine ratio greater than or equal to 300 mg/g or proteinuria >500 mg/24 hours)
Accepted
Heart failure in patients unable to tolerate ACE inhibitors

**Contraindications**
Hypersensitivity reactions, eg urticaria, angioedema.
Renal artery stenosis (bilateral, or unilateral with solitary kidney)

**Specific considerations**

### Adverse effects

- **Common:** dizziness, headache, hyperkalaemia
- **Infrequent:** first dose orthostatic hypotension, rash, diarrhoea, dyspepsia, muscle cramp, myalgia, back pain, insomnia, nasal congestion, abnormal liver function, decreased haemoglobin, renal impairment, pharyngitis
- **Rare:** cough, urticaria, angioedema, Henoch-Schönlein purpura, hepatitis, taste disturbance, migraine

### Dosage

Usually 20–40 mg once daily; can be increased if necessary to 80 mg once daily.

### Patient counselling

Same as Candesartan

### Practice points

Same as Candesartan

### Products

- **TELMISARTAN TABS 40 MG (MICARDIS®)**
- **TELMISARTAN TABS 80 MG (MICARDIS®)**

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**VALSARTAN**

### Mode of action

Same as Candesartan

### Indications

Hypertension; myocardial infarction with left ventricular failure or left ventricular systolic dysfunction

### Cautions

Hepatic impairment; renal impairment

### Contra-indications

Cirrhosis, biliary obstruction, Pregnancy, breast-feeding

### Specific considerations

- **Adverse-effects**
  - Rarely anaemia, neutropenia; very rarely taste disturbances, syncope, fatigue, cough, headache, thrombocytopenia, epistaxis, arthralgia, myalgia, and rash

### Dose

- Hypertension, usually 80 mg once daily (initially 40 mg once daily in intravascular volume depletion); if necessary increased after at least 4 weeks to 160 mg daily; elderly over 75 years, initially 40 mg once daily
- Myocardial infarction, initially 20 mg twice daily increased over several weeks to 160 mg twice daily if tolerated

### Patient counselling

Same as Candesartan

### Practice points

Same as Candesartan

### Products

- **VALSARTAN CAPS 80 MG (DIOVAN®)**
- **VALSARTAN CAPS 160 MG (DIOVAN®)**

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**02.06 NITRATES, CALCIUM-CHANNEL BLOCKERS, AND POTASSIUM-CHANNEL ACTIVATORS**

**ANGINA**

### Rationale for drug use

Provide symptom relief. Reduce risk of death or MI.

### Before starting treatment

Evaluate and manage risk factors (eg smoking, hypertension, dyslipidaemia).
Consider causes requiring specific treatment (eg aortic stenosis) and need for myocardial revascularisation procedures.
Investigate specific precipitants (eg exertion, anaemia, thyrotoxicosis).
Plan appropriate investigations.

### Drug choice
Use of low dose aspirin and treatment of dyslipidaemia and hypertension will reduce the risk of MI. Antianginal agents (nitrates, beta-blockers, calcium channel blockers, perhexiline and nicorandil) improve the balance between myocardial oxygen supply and demand and relieve of angina symptoms. There is strong evidence that beta-blockers reduce mortality after MI, and limited evidence for verapamil. Other antianginals have not been shown to reduce mortality post MI. Choice of an antianginal agent is also influenced by coexisting diseases (eg avoid beta-blockers in severe asthma; avoid verapamil and diltiazem in heart failure) and severity of angina, and may be limited by adverse effects (eg headache with nitrates).

Beta-blockers are recommended as initial therapy in the absence of contraindications. Calcium channel blockers (except short acting dihydropyridines), in particular verapamil, and long acting nitrates can be used when beta-blockers are contraindicated.

Antianginal agents may be used as single agents or in combinations.

Combine a beta-blocker with diltiazem with caution; avoid combining a beta-blocker with verapamil due to risk of severe bradycardia and heart block.

The glycoprotein IIb/IIIa inhibitors eptifibatide and tirofiban are recommended (with aspirin and heparin) for unstable angina in patients with a high risk of developing myocardial infarction. Abciximab, eptifibatide or tirofiban may also be used with aspirin and heparin in patients undergoing percutaneous coronary intervention, to reduce the immediate risk of vascular occlusion.

Revascularisation procedures are often appropriate for patients with unstable angina.

**Long-term management**

The importance of life-style changes, especially stopping smoking, should be emphasised. Patients should receive low-dose aspirin indefinitely: a dose of 75 mg daily is suitable. A statin should also be prescribed. The need for long-term angina treatment or for coronary angiography should be assessed. If there is continuing ischaemia, standard angina treatment should be continued; if not, antianginal treatment may be withdrawn cautiously at least 2 months after the acute attack.

**Nitrates**

Include glyceryl trinitrate (available as a sublingual tablet or spray, a transdermal patch, and IV infusion), isosorbide dinitrate (available as a sublingual or oral tablet) and isosorbide mononitrate (available as a controlled release tablet). Duration of action, and therefore clinical use, varies between nitrates and between formulations.

Tolerance to nitrates occurs with frequent or continuous exposure; avoid tolerance by ensuring a nitrate-free interval of 10–12 hours each day.

Short acting nitrates (sublingual isosorbide dinitrate or glyceryl trinitrate) are used to treat acute episodes of angina, or prophylactically immediately before an activity likely to precipitate angina; IV glyceryl trinitrate infusion is used for unstable angina.

Longer acting nitrates (oral isosorbide dinitrate, isosorbide mononitrate, transdermal glyceryl trinitrate) are used to prevent angina in patients with more frequent symptoms.

Nitrates may be used safely in combination with other antianginals.

**Beta-blockers**

Reduce frequency of angina, prolong exercise capacity and decrease the risk of adverse cardiac events and mortality. Beta-blockers with intrinsic sympathomimetic activity (oxprenolol, pindolol) may be less effective; they have not been found to benefit patients after MI.

Beta-blockers may be used with nitrates, nicorandil, perhexiline and dihydropyridine calcium channel blockers; use with diltiazem with caution because of risk of bradycardia; avoid using with verapamil because of risk of severe bradycardia and heart block.

Abrupt withdrawal of beta-blocker may lead to increased myocardial ischaemia, risk of infarction and sudden death; if withdrawal is required, reduce dose gradually over 2 weeks (or 4–6 weeks if the patient has been treated for many years).

**Calcium channel blockers**

Symptomatic efficacy of calcium channel blockers in angina is similar to that of beta-blockers. Only controlled release verapamil has been shown to reduce the incidence of cardiovascular events in patients with stable angina; it may decrease the risk of reinfarction and death after MI. However, it is contraindicated in patients with systolic heart failure.

Avoid combining verapamil with beta-blockers except in patients without systolic ventricular dysfunction and under close surveillance, because of additive negative effect on cardiac conduction and high risk of severe bradycardia and heart block.

Short acting formulations of nifedipine may be associated with reflex tachycardia, which may exacerbate ischaemic heart disease. They can enhance the risk of adverse cardiac events and should be avoided. Long acting nifedipine has
not been shown to decrease cardiovascular morbidity and mortality in patients with angina. Diltiazem has less negative inotropic effect than verapamil and causes less reflex tachycardia than the dihydropyridines; can be used safely with nitrates and with caution with beta-blockers (monitor for bradycardia) with heart failure.

02.6.1 Nitrates

**GLYCERYL TRINITRATE**
Also known as nitroglycerine and GTN.

**Mode of action**
Provide exogenous source of nitric oxide (which mediates vasodilator effects). Predominantly venodilators; reduce venous return and preload to the heart, reducing myocardial oxygen requirement.

**Indications**

**Contraindications**
Hypotension, hypovolaemia, hypertrophic obstructive cardiomyopathy, cardiac tamponade, aortic or mitral stenosis, cor pulmonale, marked anaemia, raised intracranial pressure Combined use with sildenafil, tadalafil or vardenafil

**Specific considerations**
G6PD deficiency: risk of haemolytic anaemia. Surgery: Remove nitrate patches before diathermy, defibrillation or cardioversion. Pregnancy: Safety is not established; may be used to assist removal of retained placenta; ADEC category B2.

**Adverse effects**
Most are due to vasodilator effects. Common: headache, flushing, palpitations, orthostatic hypotension, syncope, peripheral oedema Infrequent: contact dermatitis (topical), rebound angina

**Dosage**

**Acute angina**
Sublingual tablet, 300–600 micrograms (half to 1 tablet) repeated every 3–4 minutes until pain is resolved, to a maximum of 2 or 3 tablets over 15 minutes. Sublingual spray, 400–800 micrograms (1–2 sprays).

**Prevention of acute angina before a precipitating activity**
Sublingual tablet, 300–600 micrograms (half to 1 tablet) 5–10 minutes before activity. Sublingual spray, 400 micrograms (1 spray) 5–10 minutes before activity.

**Prevention of chronic angina**
Patch, 5 mg patch for up to 14 hours daily; may be increased up to 15 mg patch.

**Unstable angina, acute pulmonary oedema, heart failure associated with acute MI**
IV infusion 5–10 micrograms/minute, increased by 5 micrograms/minute every 3–5 minutes until desired clinical response; usual dose in heart failure is 20–80 micrograms/minute.

**Administration instructions**
Infusion: glyceryl trinitrate is adsorbed onto some plastics, eg PVC. Use glass infusion bottle and polyethylene administration set.

**Patient counselling**
Patch: Apply to clean, dry skin on the chest area or upper arm. Sublingual tablets or spray: Use during episodes of angina or before an activity expected to bring on angina. Sit or lie down before use as it may cause dizziness. Sublingual tablets: Place half to one tablet under your tongue; do not swallow it; after the pain has been relieved, you may spit out or swallow what is left of the tablet to avoid adverse effects such as headache. Call an ambulance if 2 or 3 tablets over 15 minutes do not relieve pain. It is important to store these tablets properly or they may not work as well. Keep them in the original glass bottle away from moisture, heat and light. Do not carry them close to your body. Write the date on the bottle when you open it and discard any unused tablets 3 months later.

Sublingual spray:
Prime the spray before using it for the first time by pressing the nozzle 5 times, spraying it into the air. Prime it with 1 spray if it hasn't been used for 7 days. Prime it with 5 sprays if it hasn't been used for more than 4 months. When ready to use, aim the spray under the tongue and press the nozzle once; do not inhale the spray. Call an ambulance if 2 sprays over 15 minutes do not relieve pain. This medicine may make you feel dizzy on standing. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.

**Practice points**

- sublingual glyceryl trinitrate spray has a longer shelf life than tablets; it is useful for patients with infrequent angina
- ensure a nitrate-free period of 10–12 hours each day with long acting glyceryl trinitrate (patch) to avoid tolerance
- do not stop IV infusion abruptly because of the potential for rebound symptoms
- tolerance to nitrates occurs with frequent or continuous exposure (may occur within 24 hours); avoid by ensuring a nitrate-free interval of 10–12 hours each day

**Products**

GLYCERYL TRINITRATE TRANSDERMAL  5 MG/24 HOUR (DEPONIT NT TRANSDERMAL®, NITRODERM TTS-5®)
GLYCERYL TRINITRATE TRANSDERMAL  10 MG/24 HOUR (DEPONIT NT TRANSDERMAL®, NITRODERM TTS-5®)
GLYCERYL TRINITRATE VIAL  1 MG/ML  50 ML VIAL (NITROCINE®)

**ISOSORBIDE DINITRATE**

**Mode of action**
Provide exogenous source of nitric oxide (which mediates vasodilator effects). Predominantly venodilators; reduce venous return and preload to the heart, reducing myocardial oxygen requirement.

**Indications**
Prevention and treatment of angina, Heart failure (with hydralazine)

**Contraindications**
Hypotension, hypovolaemia, hypertrophic obstructive cardiomyopathy, cardiac tamponade, aortic or mitral stenosis, cor pulmonale, marked anaemia, raised intracranial pressure
Combined use with sildenafil, tadalafil or vardenafil

**Specific considerations.**
G6PD deficiency: risk of haemolytic anaemia.
Surgery: Remove nitrate patches before diathermy, defibrillation or cardioversion.
Pregnancy: No data available; ADEC category B1
Breastfeeding: No data available.

**Adverse effects**
Most are due to vasodilator effects.
Common: headache, flushing, palpitations, orthostatic hypotension, syncope, peripheral oedema
Infrequent: contact dermatitis (topical), rebound angina

**Dosage**
Treatment of acute angina: Sublingual tablet, 5–10 mg.
Prevention of acute angina before a precipitating activity: Sublingual tablet, 5–10 mg taken 10 minutes before activity.
Prevention of chronic angina: Oral tablet, 10–40 mg up to 3 times daily.
Treatment of acute heart failure: Sublingual tablet, 5–10 mg every 2 hours or as needed.
Treatment of chronic heart failure: Oral tablet, 20–40 mg 4 times daily (with hydralazine).

**Patient counselling**
Sublingual tablets
Use during episodes of angina or before an activity expected to bring on angina.
Sit or lie down before use as the drug may cause dizziness.
Place the tablet under your tongue; do not swallow; after angina has been relieved, you may spit out what is left of the tablet to avoid adverse effects such as headache.
Call an ambulance if 2 sublingual tablets over 15 minutes do not relieve pain.

**Practice points**
tolerance to nitrates occurs with frequent or continuous exposure (may occur within 24 hours); avoid by ensuring a nitrate-free interval of 10–12 hours each day

**Products**

- **ISOSORBIDE DINITRATE TABS 5 MG (CARDIPINE®, ISOHART®, ISOKET®, ISORDIL®, PENSORDIL®)**
- **ISOSORBIDE DINITRATE TABS 10 MG (CARDIPINE®, ISOHART®, ISOKET®, ISORDIL®, PENSORDIL®, )**
- **ISOSORBIDE DINITRATE TABS 20 MG (CARDIPINE®, ISOHART®, ISOKET®, ISOMACK®, PENSORDIL®)**
- **ISOSORBIDE DINITRATE TABS 40 MG (ISOCARD®, ISOKET®, ISOMACK®, PENSORDIL®)**

### 02.06.02 Calcium Channel Blockers

**AMLODIPINE**

**Mode of action**

Amlodipine blocks inward current of calcium into cells in vascular smooth muscle, myocardium and cardiac conducting system via L-type calcium channels.

Calcium channel blockers differ in their chemical nature, sites of action and therapeutic effects. Dihydropyridines act mainly on vascular smooth muscle to reduce peripheral vascular resistance, and have minimal effect on normal myocardial cells at therapeutic doses.

Verapamil has greater cardiac effects, reducing contractility, heart rate and conduction with less effect on vascular smooth muscle.

Diltiazem acts on both cardiac and vascular smooth muscle, but it has less effect on cardiac cells than verapamil.

**Indications**

- Hypertension
- Angina

**Contraindications**

- Cardiogenic shock
- Severe bradycardia, sick sinus syndrome, second or third degree atrioventricular block (without pacemaker),

**Specific considerations ;**

- Treatment with drugs which can cause bradycardia – may further decrease heart rate and cause hypotension, monitor cardiac function
- Heart failure, significantly impaired left ventricular function
- First degree atrioventricular block: risk of worsening.
- Angina: symptoms may be exacerbated when initiating treatment as a result of reflex cardiac stimulation (increased rate and contractility).
- Hepatic impairment: May require a reduction in dosage.
- Elderly: Start treatment at a lower dose.
- Pregnancy: This drugs may produce fetal hypoxia associated with maternal hypotension, primarily with short acting preparations; ADEC category C. Nifedipine is used for threatened preterm labour.
- Breastfeeding: Limited data available for nifedipine, diltiazem and verapamil; nifedipine has a low excretion in breast milk and seems safe to use. No data for amlodipine, felodipine and lercanidipine; avoid use.

**Adverse effects**

- Most listed adverse effects occur with all calcium channel blockers.
- Adverse effect profile varies between specific calcium channel blockers according to relative effects on vascular, myocardial and conducting tissue.
- Common: peripheral oedema, rash, headache, fatigue, dizziness, flushing, nausea, abdominal pain, gingival hyperplasia
- Rare: parkinsonism, dihydropyridines, cerebral and myocardial ischaemia (following excessive fall in BP)

**Dosage**

- Initially 2.5–5 mg once daily, increased over 1–2 weeks to a maximum of 10 mg once daily.
- Elderly, hepatic impairment: Initially 2.5 mg daily.
Products
AMLODIPIN CAPS/TABS 5 MG (AS BESILATE) (AMLOCARD®, AMLOVAS®, HYPODIPINE®, LOWRAC®, LOWVASC®, MYODIPINE®, NORVASC®)

DILTIAZEM
Mode of action
Same as Amlodipine
Indications
Hypertension (controlled release), Angina
Contraindications
Cardiogenic shock
Severe bradycardia, sick sinus syndrome, second or third degree atrioventricular block (without pacemaker), hypotension (systolic BP <90 mm Hg)
Specific considerations:
Treatment with drugs which can cause bradycardia: may further decrease heart rate and cause hypotension; monitor cardiac function
Heart failure, significantly impaired left ventricular function: risk of further depression of cardiac function; use with caution.
First degree atrioventricular block: risk of worsening.
Angina: symptoms may be exacerbated when initiating treatment as a result of reflex cardiac stimulation (increased rate and contractility).
Hepatic impairment: May require a reduction in dosage.
Elderly: Start treatment at a lower dose.
Pregnancy: may produce fetal hypoxia associated with maternal hypotension, primarily with short acting preparations; ADEC category C.
Breastfeeding: Limited data available for nifedipine, diltiazem
Adverse effects
Same as Amlodipine
Dosage
Angina: Conventional product, initially 30 mg 3–4 times daily, increase as required up to 180–240 mg daily.
Controlled release products, initially 180 mg once daily; increase as required up to 360 mg once daily.
Hypertension: Controlled release products, initially 180–240 mg once daily; increase as required up to 360 mg once daily.
Dose conversion: When converting to controlled release product, use the strength nearest the total daily dose of standard formulation.
Practice points
• dihydropyridine-induced peripheral oedema does not require treatment with diuretics, which may put patient at risk of volume depletion

Products
DILTIAZEM CAPS 300 MG (AS HCL) (MONO-TILDIEM®)
DILTIAZEM TABS 90 MG (AS HCL) (BI-TILDIEM®, DILZACARD®, DILZEM®)

FELODIPINE
Mode of action
Same as Amlodipine
Indications
Hypertension, Angina
Contraindications
Cardiogenic shock
Severe bradycardia, sick sinus syndrome, second or third degree atrioventricular block (without pacemaker),
Adverse effects
Same as Amlodipine
Dosage
Initially 5 mg once daily, maintenance dose 5–10 mg once daily; maximum dose 20 mg daily.
Elderly, hepatic impairment: Initially 2.5 mg daily.
Patient counselling
Swallow tablet whole; do not crush or chew.
Avoid grapefruit as it may increase the risk of side effects with felodipine.

Practice points
- dihydropyridine-induced peripheral oedema does not require treatment with diuretics, which may put patient at risk of volume depletion

Products
FELODIPINE TABS 5 MG (PLENDIL®)
FELODIPINE TABS 10 MG (PLENDIL®)

NIFEDIPINE
Mode of action
Same as Amlodipine
Indications
Marketed: Hypertension, Angina
Accepted: Preterm labour
Contraindications
Treatment with IV salbutamol
Cardiogenic shock: Severe bradycardia, sick sinus syndrome, second or third degree atrioventricular block (without pacemaker)
Specific considerations
Same as Amlodipine
Adverse effects
Same as Amlodipine
Dosage:
Conventional tablet, initially 10–20 mg twice daily, increase to 20–40 mg twice daily.
Controlled release tablet, initially 30 mg once daily, increase to a maximum of 90 mg once daily (angina) or 120 mg once daily (hypertension).
Threatened preterm labour: Conventional tablet, 20 mg initially, repeat dose 30 minutes after first dose if uterine contractions persist. If contractions continue after 3 hours, give 20 mg every 3–8 hours until contractions cease or patient is in established labour. Continue nifedipine as controlled release tablet in following days if necessary, in dose required to stop contraction; maximum daily dose 160 mg.

Patient counselling
Swallow controlled release tablet whole; do not crush or chew.

Practice points
- nifedipine controlled release tablet 60 mg is approximately equivalent to nifedipine conventional tablets 40 mg (2x20 mg) daily
- stop nifedipine if marked hypotension or dyspnoea occur
- short acting formulations of nifedipine may be associated with reflex tachycardia, which may exacerbate ischaemic heart disease
- dihydropyridine-induced peripheral oedema does not require treatment with diuretics, which may put patient at risk of volume depletion

Products
NIFEDIPINE TABS 30 MG (ADALAT LA®)
NIFEDIPINE TABS/CAPS 20 MG (ADALAT RETARD®, CORACTEN®, EPILAT RETARD®, MACOREL RETARD®, MYOGARD RETARD®)

NIMODIPINE
Mode of action
Relaxes smooth muscle by inhibiting influx of calcium ions through voltage-operated channels. May prevent cerebral ischaemic damage from reactive vasospasm after subarachnoid haemorrhage by dilating cerebral vessels and increasing blood flow.
Indications
Prevention and treatment of ischaemic neurological deficits following subarachnoid haemorrhage
Specific considerations
Cerebral oedema, severely raised intracranial pressure, hypotension: risk of aggravation.
Hepatic impairment: Requires lower dosage; monitor BP and pulse rate.
Pregnancy: Avoid use; may cause fetal hypoxia; ADEC category C.
Breastfeeding: No data available; avoid use.

Adverse effects
Common: hypotension, bradycardia, headache, flushing, feeling of warmth, oedema, arrhythmia, elevation in liver enzymes, rash, nausea, vomiting
Infrequent: hepatitis, paralytic ileus

Dosage
IV
Co-infuse with a compatible solution, eg sodium chloride 0.9%, glucose 5% or dextran 40.
>70 kg, initially 1 mg/hour for the first 2 hours; give co-infusion solution at a rate of 20 mL/hour.
If well tolerated (ie BP stable), increase dosage up to 2 mg/hour (with an increase in the rate of co-infusion solution to 40 mL/hour) for 5–14 days.
<70 kg or labile BP or hepatic impairment, initially 0.5 mg/hour with co-infusion solution at a rate of 10 mL/hour.
Maximum 1 mg/hour.

Oral
Give for about 7 days following nimodipine infusion, or for 10–14 days if no infusion was given.
>70 kg, 60 mg every 4 hours.
<70 kg or labile BP or hepatic impairment, 30 mg every 4 hours.

Administration instructions
Give infusion via a central catheter using an infusion pump.
Do not use PVC giving sets because of the loss of nimodipine and contamination by plasticisers; use polyethylene sets.

Products
NIMODIPINE VIAL 200 MCG/ML 50 ML VIAL (NIMOTOP®)

02.06.03 Other drugs for angina

TRIMETAZIDINE
Trimetazidine hydrochloride is used in angina pectoris and in ischaemia of neurosensorial tissues as in Ménière's disease; 40 to 60 mg is given daily by mouth in divided doses.

Products
TRIMETAZIDINE TABS 20 MG (AS HCL) (VASTAREL®)

02.07 SYMPATHOMIMETICS
The properties of sympathomimetics vary according to whether they act on alpha or on beta adrenergic receptors. Adrenaline (epinephrine) acts on both alpha and beta receptors and increases both heart rate and contractility (beta₁ effects); it can cause peripheral vasodilatation (a beta₂ effect) or vasoconstriction (an alpha effect).
The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

Mode of action
Sympathomimetics partially or completely mimic the agonistic actions of noradrenaline or adrenaline on the alpha and/or beta adrenoceptors. The effect of a specific agent is determined by receptor specificity, compensatory reflexes evoked and dose.

Sympathomimetics have a range of therapeutic uses, eg treating hypotension, arrhythmias, heart failure, severe allergic reactions and bronchospasm.

Comparative information
See Table 02-01 Comparative information for sympathomimetics

Practice points
- treatment with sympathomimetics is guided by haemodynamic monitoring; individualise treatment depending on clinical response
- use is restricted to settings where close monitoring of arterial and venous pressure, and ECG can be performed
- prolonged use of sympathomimetics may result in diminution of therapeutic effect (down-regulation of receptors)
- combinations of sympathomimetics may be used
02.07.01 Inotropic Sympathomimetics

DOBUTAMINE

Mode of action
Inotropic agent; vasodilator.
The cardiac stimulants dobutamine and dopamine act on beta₁ receptors in cardiac muscle, and increase contractility with little effect on rate.

Indications
Inotropic support in acute heart failure and cardiogenic shock due to MI, open heart surgery, acute exacerbation of chronic heart failure, septic shock, positive end expiratory pressure ventilation Pharmacological stress testing of myocardial function

Contraindications
Phaeochromocytoma, ventricular arrhythmias, rapid AF

Specific considerations
Hypovolaemia: correct before treating with dobutamine.
AF: dobutamine facilitates atrioventricular conduction; risk of rapid ventricular response.
Children: Not marketed for use in children; limited information available; used in paediatric and neonatal intensive care units.
Pregnancy: No adequate studies; ADEC category B2.
Breastfeeding: Contact specialised information service

Adverse effects
Common: tachycardia, excessive increase in BP, ventricular ectopic activity
Infrequent: nausea, headache, angina, palpitations, ventricular tachycardia or fibrillation, hypotension, shortness of breath, rash, fever, eosinophilia, bronchospasm, urinary urgency, phlebitis and local inflammatory changes following extravasation
Rare: allergic reaction (sodium metabisulfite in products)

Dosage
Adjust according to clinical response; monitor BP and ECG continuously; monitor central venous or pulmonary wedge pressure and cardiac output.
Inotropic support: Initially 2.5–5 micrograms/kg/minute; increase gradually by 5 micrograms/kg/minute; maximum 40 micrograms/kg/minute.
Stress testing: 5 micrograms/kg/minute increasing in steps of 5 micrograms/kg/minute every 5–10 minutes to maximum of 20 micrograms/kg/minute.

Administration instructions
Dilute before use in glucose 5% or sodium chloride 0.9%. Do not add to sodium bicarbonate or other strongly alkaline solutions.

Practice points
- treatment with sympathomimetics is guided by haemodynamic monitoring; individualise treatment depending on clinical response
- use is restricted to settings where close monitoring of arterial and venous pressure, and ECG can be performed
- prolonged use of sympathomimetics may result in diminution of therapeutic effect (down-regulation of receptors)
- combinations of sympathomimetics may be used

Products
DOBUTAMINE VIAL 250 MG/VIAL (AS HCL) 20 ML VIAL (DOBUTAMINE®, DOBUTREX®)

DOPAMINE

Mode of action
Vasodilator at low dose; vasoconstrictor at higher doses; positive inotrope and chronotrope at high dose.
Sympathomimetics partially or completely mimic the agonistic actions of noradrenaline or adrenaline on the alpha and/or beta adrenoceptors. The effect of a specific agent is determined by receptor specificity, compensatory reflexes evoked and dose.
Sympathomimetics have a range of therapeutic uses, eg treating hypotension, cardiac arrhythmias, heart failure, severe allergic reactions and bronchospasm.
**Indications**
Inotropic support in acute heart failure and cardiogenic shock due to MI, open heart surgery, septic shock, positive end expiratory pressure ventilation, acute exacerbation of chronic heart failure

**Contraindications**
Phaeochromocytoma, tachyarrhythmias
Manufacturer contraindicates treatment with halogenated hydrocarbon general anaesthetics or ergot alkaloids

**Specific considerations**
Hypovolaemia: correct before using dopamine.
Hyperthyroidism, occlusive vascular disease, cardiac ischaemia: increase risk of cardiovascular adverse effects.
Acidosis, hypercapnia, hypoxia: may reduce the effectiveness and/or increase the incidence of adverse effects of dopamine.
Pulmonary hypertension: may worsen due to dopamine-induced pulmonary vasoconstriction.
Treatment with MAOIs or moclobemide: may prolong and intensify effect of dopamine; begin with 10% of the usual dopamine dose in patients who have received a MAOI within the previous 2–3 weeks, or moclobemide in the previous 48 hours, then titrate cautiously.

**Children**
Not marketed for use in children; limited information available; used in paediatric and neonatal intensive care units.

**Pregnancy**
Limited human data available; ADEC category B3.

**Dosage**
Adjust dose according to clinical response. Excessive dosage may be shown by disproportionate rise in diastolic pressure (marked decrease in pulse pressure); infusion rate should be decreased or ceased.
Initially 2.5–5 micrograms/kg/minute; increase gradually by 5–10 micrograms/kg/minute. Maintenance, 20–50 micrograms/kg/minute up to a maximum of 60 micrograms/kg/minute.

**Administration instructions**
Dilute before use, but not in alkaline solutions (inactivates dopamine); infuse into a large vein.

**Practice points**
Same as dobutamine

**Products**
DOPAMINE AMPS 40 MG/ML (AS HCL) 5 ML VIAL (DOPAMINE®)

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**ISOPRENAINE**

**Mode of action**
Beta-agonist; increases cardiac output by its positive chronotropic and inotropic actions. Tends to maintain or increase systolic BP; decreases diastolic BP by lowering peripheral vascular resistance; increases automaticity and AV nodal conduction. Usually improves coronary blood flow.

**Indications**
Heart block, Bradycardia with haemodynamic compromise, Adjunct in cardiogenic, septic, and hypovolaemic shock

**Contraindications**
Tachycardia, Phaeochromocytoma, Allergy to isoprenaline or sulfites

**Specific considerations**
Hypovolaemia: correct before using isoprenaline.
Recent MI: risk of increased myocardial work; may increase infarct size and ventricular ectopic activity; avoid use.
Ischaemic heart disease: isoprenaline may exacerbate angina.
Hypertension: isoprenaline may increase systolic BP; monitor closely and adjust dose if necessary.
Hyperthyroidism: risk of tachycardia and arrhythmias.
Children: Use is limited to paediatric intensive care.

**Pregnancy**
ADEC category A.

**Breastfeeding**
No data available.

**Adverse effects**
Common: palpitations, tachycardia, hypotension, flushing, headache, nervousness, restlessness, fine tremor
Infrequent: arrhythmias, angina, hypertension, nausea, dry mouth, insomnia, rash, itch, wheeze
Rare: allergic reactions (sodium bisulfite in injection)

**Dosage**
Adult: IV injection, 20 micrograms; subsequent bolus, 10–200 micrograms, titrate to ventricular response. IV infusion, 0.5–10 micrograms/minute, titrate to clinical response.
Child: IV infusion, 0.05–2 micrograms/kg/minute.

**Administration instructions**
IV injection, dilute 0.2 mg (1 mL) to 10 mL (20 micrograms/mL) with sodium chloride 0.9% or glucose 5%.
IV infusion, dilute 2 mg (10 mL) to 50 mL (40 micrograms/mL) or 500 mL (4 micrograms/mL) with glucose 5%.

**Products**
ISOPRENALINE AMPS 0.25 MG/ML 1 ML AMP (ISUPRIL®)

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**02.07.02 Cardiopulmonary Resuscitation**

In cardiac arrest adrenaline (epinephrine) 1 in 10 000 (100 micrograms/mL) is recommended in a dose of 10 mL by intravenous injection, preferably through a central line. If injected through a peripheral line, the drug must be flushed with at least 20 mL sodium chloride 0.9% injection (to aid entry into the central circulation). Intravenous injection of amiodarone 300 mg (from a prefilled syringe or diluted in glucose intravenous infusion 5%) should be considered after adrenaline to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. Atropine 3 mg by intravenous injection as a single dose is also used in cardiopulmonary resuscitation to block vagal activity.

**ADRENALINE**

Also known as epinephrine.

**Mode of action**
Nonselective adrenergic agonist. Positive inotrope and chronotrope (beta_1 receptors); vasodilator at low dose (beta_2 receptors); vasoconstrictor at high dose (alpha receptors). Bronchial smooth muscle relaxant (beta_2 receptors). Stabilises mast cells.

Sympathomimetics partially or completely mimic the agonistic actions of noradrenaline or adrenaline on the alpha and/or beta adrenoceptors. The effect of a specific agent is determined by receptor specificity, compensatory reflexes evoked and dose.

Sympathomimetics have a range of therapeutic uses, eg treating hypotension, cardiac arrhythmias, heart failure, severe allergic reactions and bronchospasm.

**Indications**
Cardiac arrest, Inotropic support in acute heart failure and cardiogenic shock, acute exacerbation of chronic heart failure, septic shock, positive end expiratory pressure ventilation, Severe allergic reactions including anaphylactic shock and life-threatening angioedema and bronchospasm, Adjunct in local anaesthesia

**Contraindications**
Phaeochromocytoma, Tachyarrhythmias, Local use in anaesthesia of fingers, toes, ears, nose or genitalia

**Specific considerations**
Hypovolaemia: correct before using adrenaline.
Heart disease (ischaemic heart disease, heart failure, arrhythmias): increases risk of arrhythmias, angina, myocardial ischaemia.
Hypertension, hyperthyroidism, cardiovascular disease, diabetes: adverse reactions are more likely.
Oclusive or cerebrovascular disease: increases risk of peripheral ischaemia or stroke.
Acidosis, hypercapnia or hypoxia: may reduce the effectiveness and/or increase the incidence of adverse effects of adrenaline.
Aortic stenosis, hypertrophic cardiomyopathy: may increase outflow obstruction.
Pulmonary hypertension: may exacerbate due to pulmonary vasoconstriction.
Closed angle glaucoma: increases intracocular pressure due to pupillary dilation.
Pregnancy: Use if required, but adrenaline may delay the second stage of labour; ADEC category A.
Breastfeeding: No data available.

**Adverse effects**
Common: anxiety, headache, fear, palpitations, tachycardia, restlessness, tremor, dizziness, dyspnoea, weakness, sweating, pallor, hyperglycaemia
Infrequent: excessive increase in BP, ventricular arrhythmias, pulmonary oedema, angina, peripheral ischaemia and necrosis (at infusion site or in local anaesthesia of fingers, toes, ears, nose or genitalia)
Rare: allergic reaction (sodium metabisulfite in products)
Overdose or rapid IV administration: cardiac arrhythmias (ventricular and supraventricular), severe hypertension, cerebral haemorrhage, pulmonary oedema

**Dosage**
Adjust according to clinical response. Monitor BP and ECG continuously; monitor central venous or pulmonary wedge pressure and cardiac output.

**Cardiac arrest**
Adult: IV, 0.5–1 mg. IV infusion, 1–4 micrograms/minute. Endotracheal tube, 1 mg.
Child: IV, 0.01 mg/kg. IV infusion, 0.05–1 microgram/kg/minute. Endotracheal tube, 0.1 mg/kg.

**Administration instructions**
Do not use if the solution contains a precipitate or is brown.

**Practice points**
Same as dobutamine

**Products**
EPINEPHRINE AMPS 100 MCG/ML 10 ML AMP (ADRENALINE®)

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**02.08 ANTICOAGULANTS AND PROTAMINE**

**02.08.01 Parenteral anticoagulants**

**HEPARIN**
Heparin initiates anticoagulation rapidly but has a short duration of action. It is now often referred to as being standard or unfractionated heparin to distinguish it from the low molecular weight heparins, which have a longer duration of action. For patients at high risk of bleeding, heparin is more suitable than low molecular weight heparin because its effect can be terminated rapidly by stopping the infusion.

**Mode of action**
Inactivate clotting factors IIa (thrombin) and Xa by binding to antithrombin III; danaparoid and LMWHs have a much greater effect on factor Xa than on thrombin.

**Indications**
Treatment of arterial thromboembolism (acute MI, unstable angina, peripheral arterial occlusion)
Prevention of venous thromboembolism (deep venous thrombosis and pulmonary embolism) in surgical and high risk medical patients
Treatment of venous thromboembolism
Prevention of extracorporeal thrombosis during haemodialysis
Treatment of unstable angina and non-Q-wave MI
Treatment of acute MI and peripheral arterial occlusion
Prevention of arterial thrombosis during coronary angioplasty
Prevention of reocclusion after coronary angioplasty
Prevention of extracorporeal thrombosis during cardiopulmonary bypass
Treatment of disseminated intravascular coagulation (DIC)
Pregnancy when full anticoagulation required (seek specialist advice)

**Contraindications**
Previous severe thrombocytopenia with heparin or LMWH; danaparoid may be used. Bleeding disorders, including haemophilia, Thrombocytopenia, Peptic ulcer, Cerebral haemorrhage. Severe uncontrolled hypertension, Severe hepatic disease, including oesophageal varices, Bacterial endocarditis, Major trauma or recent surgery (particularly at sites where bleeding would pose a serious risk, eg eye or CNS)

**Specific considerations**
Concurrent use of heparins and spinal or epidural anaesthesia, analgesia or lumbar puncture increases the risk of intraspinal haematoma, which may cause paralysis; if possible avoid using heparins for 12 hours before and after procedure, and for 6 hours after catheter removal; if used together monitor for signs and symptoms of neurological damage.
Treatment with other drugs which can affect the clotting process: may increase the risk of bleeding; monitor closely. Use low dose aspirin where indicated.
Intrathecal or epidural analgesia or anaesthesia, or lumbar puncture: avoid use; risk of epidural haematoma which may cause paralysis; if procedure considered necessary, seek specialist advice.
Renal impairment: Use LMWHs (dalteparin, enoxaparin) with caution, monitor clinical condition and antifactor Xa...
levels; consider dosage reduction when creatinine clearance is <30 mL/minute, see also Enoxaparin.

**Hepatic impairment:** Avoid use in severe impairment.

**Elderly:** Check renal function; dosage reduction may be required LMWHs.

**Pregnancy:** Heparin and LMWHs can be used to treat thromboembolism during pregnancy; LMWHs are not recommended in pregnant women with prosthetic heart valves; danaparoid has been used in a small number of cases; seek specialised advise; all heparins are ADEC category C.

**Breastfeeding:** Safe to use.

### Adverse effects

**Common:** bruising and pain at injection site, hyperkalaemia, mild reversible thrombocytopenia (does not necessarily indicate increased risk for severe thrombocytopenia)

**Infrequent:** transient elevation of liver transaminases, haemorrhage, severe thrombocytopenia

**Rare:** skin necrosis (usually at injection site), osteoporosis and alopecia with long term use, allergic reactions including urticaria and anaphylaxis

**Severe thrombocytopenia:** Immune-mediated thrombocytopenia occurs in <1% of patients with short term use. It may result in major ischaemic complications (eg stroke, limb ischaemia), bleeding or death. Withhold heparin or LMWH if platelet count drops 30–50% below baseline substitute alternative anticoagulant. If heparin-induced thrombocytopenia is confirmed, future use of heparin or LMWH is contraindicated.

### Comparative information

**Safety:** Bleeding incidence is similar for heparin and LMWHs. Protamine is only partially effective in reversing over-anticoagulation with LMWHs.

In renal impairment the risk of severe bleeding is higher with LMWHs than with heparin; consider reducing the dose of LMWHs in severe renal impairment (see Enoxaparin).

Severe HIT incidence is lower with LMWHs than with heparin; LMWHs should not be used as an alternative to heparin in HIT because cross-reactivity occurs in 90% of cases.

The incidence is even lower with danaparoid; it is used for treatment of HIT and as an anticoagulant in patients with previous HIT; cross-reactivity occurs in 10% of cases.

**Osteoporosis,** the risk of osteoporosis associated with long term therapeutic use seems lower with LMWHs than with heparin.

**Prevention of thromboembolism**

In general surgery heparin and LMWHs have similar efficacy in preventing VTE; LMWHs have a longer half-life (3–6 hours) than heparin (60 minutes), require only once daily administration but cost more.

In orthopaedic surgery LMWHs are more effective than heparin or warfarin in the prevention of thromboembolism. Enoxaparin is marketed for prevention of VTE in medical patients bedridden due to acute illness; reserve for patients with several predisposing factors for VTE (elderly people, acute infection, acute heart failure, respiratory insufficiency) and at low risk of bleeding.

Long term treatment with LMWHs (dalteparin) may be more effective than oral anticoagulants in preventing recurrent VTE in patients with cancer.

**Treatment of thromboembolism**

In trials comparing hospital treatment of deep venous thrombosis, LMWHs were at least as effective as heparin in preventing recurrent thromboembolism and in reducing overall mortality.

Trials comparing heparin (given IV in hospital) with LMWH (given to outpatients) have shown no significant differences in recurrence of thromboembolism, major bleeding or overall mortality.

Heparin may be given by continuous IV infusion or twice daily SC injections; LMWHs are given as once or twice daily (depending on product used) SC injections.

**Unstable angina and non-Q-wave MI**

LMWHs are approved for use in unstable angina and non–Q-wave MI. Enoxaparin appears to be slightly more effective than heparin in reducing the combined endpoint of death or MI but it increases the risk of major bleeding.

**Monitoring requirements**

Monitor platelet count on days 0, 3 and 5, then on alternate days if treatment is continued. Severe HIT typically occurs between days 5 and 10 of treatment but may occur earlier if patient has been previously exposed to heparin.

**Heparin**

Monitor APTT; reference range varies with APTT reagent and is usually about 1.5–2.5 times the control value. Check local guidelines.

**LMWH and danaparoid**

Consider monitoring antifactor Xa in patients at high risk of bleeding (eg multiple trauma, renal impairment, thin or obese patients, pregnant women) or if overdose is suggested by bleeding; there is no evidence, however, that monitoring reduces bleeding risk.
Dosage
Prevention of venous thromboembolism in general surgery
SC, 5000 units 2 hours before surgery, then 5000 units 2–3 times daily for 7–10 days or until mobilised.
Prevention of venous thromboembolism in high risk medical patients
SC, 5000 units 2–3 times daily for 7–10 days or until mobilised.
Treatment of venous and arterial thromboembolism
5000 units IV bolus, followed by either IV infusion 1000–2000 units/hour or 15 000–20 000 units SC every 12 hours. Adjust doses according to APTT.
Children and smaller adults, alternative regimen of 5000 units IV bolus, followed by IV infusion 15–25 units/kg/hour, adjusted according to APTT.

Patient counselling
Report any signs of bleeding, eg nose bleeds, black or tarry bowel motions, or unexplained bruising immediately.

Practice points
- heparin is available as a sodium or calcium salt; there is little difference in their effects
- an unexpectedly high APTT may be due to blood sample being taken from same limb as heparin infusion
- use heparin IV if an invasive procedure is anticipated as the anticoagulant effect diminishes more quickly after stopping
- do not give IM because of risk of haematoma
- avoid use of heparinised saline to maintain patency of peripheral venous cannulae; use increases risk of heparin-induced thrombocytopenia without improved efficacy over 0.9% sodium chloride flushes

Products
HEPARIN SODIUM AMPS/VIAL  25,000 IU/ML  5 ML AMP OR VIAL (HEPARIN®, HIKMA HEPARIN®)
HEPARIN SODIUM VIAL  1,000 IU/ML  5 ML VIAL (HEPARIN®, HIKMA HEPARIN®)

ENOXAPARIN
A low Molecular weight Heparin

Mode of action
Inactivate clotting factors IIa (thrombin) and Xa by binding to antithrombin III; danaparoid and LMWHs have a much greater effect on factor Xa than on thrombin.

Indications
Marketed
Prevention of VTE in surgical patients and in medical patients bedridden due to acute illness
Treatment of venous thrombosis
Prevention of extracorporeal thrombosis during haemodialysis
Treatment of unstable angina and non–Q-wave MI
Accepted :Pregnancy when full anticoagulation required (seek specialist advice), Treatment of pulmonary embolism

Contraindications
Previous severe thrombocytopenia with heparin or LMWH; danaparoid may be used, Bleeding disorders, including haemophilia, Thrombocytopenia, Peptic ulcer, Cerebral haemorrhage, Severe uncontrolled hypertension, Severe hepatic disease, including oesophageal varices, Bacterial endocarditis, Major trauma or recent surgery (particularly at sites where bleeding would pose a serious risk, eg eye or CNS) breast –feeding

Specific considerations
Concurrent use of heparins and spinal or epidural anaesthesia, analgesia or lumbar puncture increases the risk of intraspinal haematoma, which may cause paralysis; if possible avoid using heparins for 12 hours before and after procedure, and for 6 hours after catheter removal; if used together monitor for signs and symptoms of neurological damage.
Treatment with other drugs which can affect the clotting process: may increase the risk of bleeding; monitor closely. Use low dose aspirin where indicated.
Renal impairment: Use with caution and monitor clinical condition and antifactor Xa levels; reduce dose when creatinine clearance <30 mL/minute. Avoid in endstage renal disease.
Hepatic impairment: Avoid use in severe impairment.
Elderly: Check renal function; dosage reduction may be required.

Pregnancy: Heparin and LMWHs can be used to treat thromboembolism during pregnancy; LMWHs are not recommended in pregnant women with prosthetic heart valves; danaparoid has been used in a small number of cases; contact specialised information centre; all heparins are ADEC category C.
Breastfeeding: Safe to use.

**Adverse effects**
Common: bruising and pain at injection site, hyperkalaemia, mild reversible thrombocytopenia (does not necessarily indicate increased risk for severe thrombocytopenia)
Infrequent: transient elevation of liver transaminases, haemorrhage, severe thrombocytopenia.
Rare: skin necrosis (usually at injection site), osteoporosis and alopecia with long term use, allergic reactions including urticaria and anaphylaxis
Severe thrombocytopenia: Immune-mediated thrombocytopenia occurs in <1% of patients with short term use. It may result in major ischaemic complications (eg stroke, limb ischaemia), bleeding or death. Withhold heparin or LMWH if platelet count drops 30–50% below baseline. If heparin-induced thrombocytopenia is confirmed, future use of heparin or LMWH is contraindicated.

**Dosage**
Prevention of venous thromboembolism
Surgical patients, moderate risk, 20 mg SC daily for 7–10 days or until mobilised, starting 2 hours before surgery. Surgical patients, high risk, 40 mg SC daily for 7–10 days or until mobilised, starting 12 hours before surgery. May be continued up to 30 days after total hip replacement surgery.
Medical patients, 40 mg SC daily for 6–14 days or until mobilised.
Renal impairment, 20 mg SC once daily when creatinine clearance <30 mL/minute.

Treatment of venous thrombosis
1 mg/kg SC twice daily, or 1.5 mg/kg once daily, for 5–10 days.
Renal impairment, 1 mg/kg SC once daily when creatinine clearance <30 mL/minute.
Prevention of extracorporeal thrombosis during haemodialysis
1 mg/kg into the arterial line of the dialysis circuit at the start of session; reduce dose in patients at high risk of haemorrhage.
Treatment of unstable angina, non–Q-wave MI
1 mg/kg SC twice daily for up to 8 days, with aspirin 75–300 mg daily.

**Dose equivalence**
1 mg is approximately equivalent to 100 units of antifactor Xa activity.

**Patient counselling**
Report any signs of bleeding, eg nose bleeds, black or tarry bowel motions, or unexplained bruising immediately.

**Practice points**
- preferably avoid in end-stage renal disease because of long half-life and high risk of bleeding
- use heparin IV if an invasive procedure is anticipated as the anticoagulant effect diminishes more quickly after stopping
- do not give IM because of risk of haematoma
- avoid use of heparinised saline to maintain patency of peripheral venous cannulae; use increases risk of heparin-induced thrombocytopenia without improved efficacy over 0.9% sodium chloride flushes

**Products**
ENOXAPARIN SYRINGE 20 MG/ML (2,000 IU) 0.2 ML SYRINGE (CLEXANE®)
ENOXAPARIN SYRINGE 40 MG/ML (4,000 IU) 0.4 ML SYRINGE (CLEXANE®)
ENOXAPARIN SYRINGE 60 MG/ML (6,000 IU) 0.6 ML SYRINGE (CLEXANE®)
ENOXAPARIN SYRINGE 80 MG/ML (8,000 IU) 0.8 ML SYRINGE (CLEXANE®)

**TINZAPARIN**

**Uses and Administration**
Tinzaparin sodium is a low-molecular-weight heparin with anticoagulant properties. It is used in the treatment and prophylaxis of venous thromboembolism and to prevent clotting during extracorporeal circulation.

**Dosage:**
For prophylaxis of venous thromboembolism during general surgical procedures 3500 units of tinzaparin sodium are given by subcutaneous injection 2 hours before the procedure, followed by 3500 units once daily for 7 to 10 days. In patients undergoing orthopaedic surgery a dose of 50 units/kg has been recommended; alternatively, a dose of 4500 units may be given 12 hours before surgery, followed by 4500 units once daily. For the treatment of venous thromboembolism tinzaparin sodium is given in a dose of 175 units/kg by subcutaneous injection once daily for at least 6 days and until adequate oral anticoagulation is established.
For prevention of clotting in the extracorporeal circulation during haemodialysis, tinzaparin sodium may be administered into the arterial side of the dialyser or intravenously. The dialyser may be primed with 500 to 1000 mL...
sodium chloride 0.9% containing 5000 units tinzaparin sodium/litre. For dialysis sessions lasting less than 4 hours a single dose of 2000 to 2500 units tinzaparin sodium is given; for longer sessions an initial dose of 2500 units is followed by an infusion of 750 units/hour.

**Adverse Effects**
See under heparin

**Contra-indications**
See under heparin, breast-feeding for Low-molecular-weight Heparins

**Products**
- Tinzaparin 4,500 IU/PFS 0.45 ML PFS (INNOHEP®)
- Tinzaparin 14,000 IU/PFS 0.70 ML PFS (INNOHEP®)
- Tinzaparin 18,000 IU/PFS 0.90 ML PFS (INNOHEP®)

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**02.08.02 Oral anticoagulants**

**WARFARIN**

**Mode of action**
Inhibits synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and the antithrombotic factors protein C and protein S.

**Indications**
- Prevention and treatment of venous thromboembolism (deep venous thrombosis and pulmonary embolism)
- Prevention of thromboembolism in patients with prosthetic heart valves
- Primary prevention of stroke in patients with AF associated with mitral valvulopathy or other risk factors
- Secondary prevention of stroke in patients with AF
- Prevention of thromboembolism before and after cardioversion
- Prevention of stroke in patients with previous MI and increased embolic risk

**Contraindications**
- Bleeding disorder, Previous GI bleeding, Haemorrhagic retinopathy, intracerebral aneurysm or haemorrhage, Severe hypertension, Bacterial endocarditis, Alcoholism, Unsupervised dementia, Frequent falls

**Specific considerations**
- Recent surgery, heart failure, thyrotoxicosis: increase risk of bleeding.
- Intrathecal or epidural analgesia or anaesthesia, or lumbar puncture: avoid use; risk of epidural haematoma which may cause paralysis; if procedure considered necessary, seek specialist advice.
- Treatment with drugs which can affect the clotting process: may increase the risk of bleeding; avoid combinations or monitor closely. (Some drugs which affect platelet function are used with warfarin in selected patients at high risk for thromboembolism.)
- Renal impairment: Use with caution; increased risk of bleeding.
- Hepatic impairment: Use with caution; increased risk of bleeding.
- Surgery: It is safe to continue warfarin in people at high risk of thromboembolism where there is a low risk of significant bleeding, eg endoscopy, minor dental and dermatological procedures.
- Stop warfarin 4–5 days before elective surgery to allow the INR to return to normal; give IV heparin or SC LMWH.
- Elderly: Increased risk of bleeding; lower dosage may be required.
- Pregnancy: Avoid use except perhaps in women with prosthetic heart valves; risk of teratogenicity and of fetal or placental haemorrhage; ADEC category D.
- Breastfeeding: Safe to use.

**Adverse effects**
- Common: bleeding
- Rare: skin necrosis, purple discoloration of toes, allergic reactions, alopecia, fever, rash, nausea, vomiting, diarrhoea, hepatic dysfunction

**Dosage**
- Usually 5 mg daily for 2 days then adjust according to INR (see Target INR below). Usual maintenance dose, 1–10 mg daily, taken at the same time each day; duration of treatment varies with indication.
- Target INR
  - 3.0–4.5 for older model mechanical heart valves.
  - 2.5–3.5 for newer model, less thrombogenic mechanical heart valves.
  - 2.0–3.0 for all other indications.

**Patient counselling**
- Take tablets at about the same time every day; use a calendar or 'anticoagulant book' to keep a record of your dose
and to mark off the date immediately after taking dose.
Always take the same brand of warfarin tablets.

Eat normally, without varying your diet too much, to keep your intake of vitamin K stable.
Avoid excessive alcohol consumption; 1–2 standard drinks per day is generally safe.

Tell your doctor and pharmacist that you are taking warfarin before starting or stopping any medication or taking herbal or OTC products.

Tell your dentist, podiatrist, physiotherapist or chiropractor that you are taking warfarin.
You need regular blood tests with this medication; call for result within 24 hours of the test and before the next dose, in case it needs adjusting.
Extra blood tests may be needed while you have any other serious illness.
Tell your doctor immediately if you have any bruising, bleeding, pink, red or dark red urine, or red or black faeces.

**Practice points**
- avoid use if compliance is likely to be poor
- stop treatment if skin lesions appear
- consider use of a warning bracelet or necklace
- advise patients of the intended duration of anticoagulation, and the potential risks of stopping treatment without medical advice
- give patients an ‘anticoagulant book’ to keep a record of their warfarin dose and INR results
- full effect of a dose change is not seen for 2–3 days
- the different brands have not been shown to be bioequivalent and should not be interchanged
- warfarin has a low therapeutic index; many drugs interact with warfarin and may decrease its efficacy or increase the risk of bleeding; it is prudent to monitor the INR when changing drug treatment

**Monitoring requirements**
- determine INR shortly before commencing warfarin, and then daily or on alternate days until INR is stable in the therapeutic range; in the long term determine INR at regular intervals of no more than 4 weeks
- determine INR more frequently if there are changes in the patient's condition, including intercurrent illness (eg heart failure, hepatic disease, GI disturbances, infections, thyroid disorders), concurrent drug administration, a change in the amount of alcohol consumed, or a change of diet (eg green leafy vegetable consumption)

**Over-anticoagulation with warfarin**
- use vitamin K to treat over-anticoagulation with warfarin (injection is commonly used orally for the small doses required)
- different recommendations have been published but have not been formally compared; local guidelines should be followed where they exist
- the anticoagulant effect of warfarin may be difficult to re-establish for several days to weeks after large doses of vitamin K; if intending to restart warfarin, use the lowest possible dose of vitamin K (see below)
- if over-anticoagulated (adapted from recommendations from the Australasian Society of Thrombosis and Haemostasis):
  - unexpected bleeding at therapeutic INR, investigate for underlying cause
  - INR <5 (no significant bleeding), lower the dose or omit next warfarin dose; resume warfarin at lower dose when INR is therapeutic
  - INR 5–9 (no significant bleeding), stop warfarin; give vitamin K (1–2.5 mg oral or 0.5–1 mg IV) if bleeding risk is high; measure INR within 24 hours and resume warfarin at lower dose when INR is therapeutic
  - INR >9 (no significant bleeding), stop warfarin and give vitamin K (2.5–5 mg oral or 1 mg IV); measure INR after 6–12 hours and resume warfarin at lower dose when INR is therapeutic; if bleeding risk is high consider giving a concentrate of factors II, IX and X (prothrombin complex), with factor VII if available, or fresh frozen plasma
  - serious bleeding, stop warfarin; give IV vitamin K (5–10 mg) and a concentrate of factors II, IX and X (prothrombin complex), with factor VII if available, or fresh frozen plasma; assess patient continually until INR <5 and bleeding stops

**Products**

**WARFARIN TABS 5 MG (ORFARIN®)**

**02.08.03 Protamines**
**PROTAMINE**
Heparin antagonist

**Mode of action**
Combines with heparin to form a stable inactive complex, reversing the anticoagulant effect of heparin; protamine is an anticoagulant at high doses.

**Indications**
Counteract anticoagulant effect of LMWH or heparin (eg in cases of severe haemorrhage or after cardiopulmonary bypass)

**Specific considerations**
Fish allergy or those who have previously received protamine (eg protamine insulin): increased risk of allergy.
Pregnancy: No data available; ADEC category B2.
Breastfeeding: No data available; polypeptide, should not diffuse into breast milk; will be destroyed by acid in stomach.

**Adverse effects**
Common: sensation of warmth, flushing, nausea, vomiting, lassitude
Infrequent: hypotension, bradycardia, dyspnoea (especially if given rapidly), allergic reaction, rebound bleeding with excessive doses

**Dosage**
1 mg slow IV injection over 10 minutes neutralises 100 units of heparin when given within 15 minutes of heparin. If time since heparin is >15 minutes, less protamine is required as heparin is excreted rapidly.
1 mg slow IV injection over 10 minutes may partially neutralise the haemorrhagic effect of 100 IU of dalteparin or 1 mg of enoxaparin. Protamine neutralises the antithrombin activity of LMWH but only partially neutralises the antifactor Xa effect.
Maximum: 50 mg/dose.

**Products**

02.09 ANTIPLATELET DRUGS

Antiplatelet drugs inhibit platelet aggregation. They are used in the management of arterial thrombosis (clots initially made of platelets); they are not used in management of VTE (fibrin clots).

**Comparative information**
See Table 02-08 Indications for antiplatelet agents

**Aspirin**
Low dose aspirin is recommended for prevention of serious vascular events, including MI and stroke, in patients at high risk (eg acute and post-MI, angina, peripheral arterial disease, stroke, AF). In patients with no previous cardiovascular disease, weigh benefit in terms of cardiovascular prevention against risk of GI and intracranial bleeding.

**Dipyridamole**
It is used with warfarin for the prevention of thromboembolism in patients with prosthetic heart valves. It is also marketed for secondary prevention of stroke in combination with aspirin. Further data are needed to confirm the superiority of this combination over aspirin alone.

**Clopidogrel**
It is approved for acute coronary syndromes without ST-segment elevation in combination with aspirin; it decreases risk of cardiovascular events but increases risk of major bleeding.
It is also approved for prevention of thromboembolism in patients with symptomatic atherosclerosis (recent ischaemic stroke, recent MI or intermittent claudication). It is slightly more effective than aspirin, especially in patients with intermittent claudication; high cost limits its use.
In patients with a history of aspirin-induced ulcer bleeding, clopidogrel causes more recurrent ulcer bleeding than aspirin combined with a PPI.
The risk of major bleeding with the combination of aspirin and clopidogrel compared with clopidogrel alone outweighs any benefit in prevention of major vascular events in patients with a recent TIA or stroke.
Clopidogrel should be initiated in hospital inpatients only.

**Ticlopidine**
Avoid ticlopidine because of its severe haematological adverse effects (1% severe neutropenia).

**Glycoprotein IIb/IIIa receptor inhibitors**
Abciximab, eptifibatide, tirofiban are used with heparin and low dose aspirin to prevent ischaemic cardiac
complications following percutaneous transluminal coronary intervention (abciximab, eptifibatide), and in patients with unstable angina or non-Q-wave MI (eptifibatide, tirofiban).

**CLOPIDOGREL**

**Mode of action**
Clopidogrel should be initiated in hospital inpatients only.
Inhibits binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation.

**Indications**
Marketed: Prevention of vascular ischaemic events in patients with symptomatic atherosclerosis (recent ischaemic stroke, recent MI or peripheral arterial disease with intermittent claudication)
Acute coronary syndrome without ST-segment elevation (with aspirin)
Accepted: Prevention of thromboembolism after placement of intracoronary stent (with aspirin)

**Contraindications**
Active internal bleeding
Intraocular lesions at risk of bleeding: use with caution.
Treatment with other drugs which can affect the clotting process: may increase the risk of bleeding; monitor closely.
Use with low dose aspirin where indicated.
Hepatic impairment: Avoid use in severe impairment, use with caution in moderate impairment; increased risk of bleeding.
Surgery: Stop at least 5 days before planned surgery or dental procedures if an antiplatelet effect is not desired; stop at least 5 days before coronary artery bypass surgery.
Pregnancy: Avoid use; no data available; ADEC category B1.
Breastfeeding: Use may be acceptable or consider aspirin.

**Adverse effects**
Common: bleeding (may be severe including GI bleeding), diarrhoea, rash
Infrequent: intracranial bleeding, GI ulcer
Rare: thrombotic thrombocytopenic purpura, aplastic anaemia, thrombocytopenia, neutropenia, allergic reactions including angioedema and erythema multiforme

**Dosage**
Prevention of vascular ischaemic events: 75 mg daily.
Acute coronary syndrome: Loading dose 300 mg, then 75 mg once daily with aspirin; continue for at least 1 month and up to 12 months.
Placement of coronary stent: Loading dose 300 mg at least 6 hours before the procedure, then 75 mg once daily with aspirin; continue for at least 1 month and up to 12 months.

**Practice points**
- do not combine aspirin with clopidogrel in patients with a recent TIA or stroke; the risk of major bleeding with this combination outweighs any benefit
- optimal duration of treatment in acute coronary syndrome and after placement of coronary stent is debated; longer treatment is recommended with a drug-eluting stent than with a bare-metal stent

**Products**
CLOPIDOGREL TABS 75 MG (AS HYDROGEN SULFATE) (PLAVIX®)

**TICLOPIDINE**

**Mode of action**
Interferes with platelet membrane function by inhibiting ADP-induced platelet–fibrinogen binding and subsequent platelet–platelet interactions.

**Indications**
Secondary prevention of ischaemic stroke and TIA in patients intolerant of or unresponsive to aspirin
Prevention of thromboembolism after placement of intracoronary stent (with aspirin)

**Contraindications**
Bleeding disorders, eg thrombocytopenia, haemophilia, von Willebrand's disease
Local haemorrhagic lesions, eg peptic ulcer, epistaxis, menorrhagia, haemorrhagic stroke
Blood dyscrasias, eg neutropenia, agranulocytosis, leucopenia, thrombocytopenia

**Specific considerations**
Treatment with other drugs which can affect the clotting process: may increase the risk of bleeding; monitor closely. Use with low dose aspirin where indicated.
Renal impairment: Avoid use in severe impairment; increased risk of bleeding.
Surgery: Stop 10–14 days before planned surgery or dental procedures if an antiplatelet effect is not desired.
Children: No data available on use in children <18 years of age.
Pregnancy: Contact specialised information service; ADEC category B1.
Breastfeeding: Avoid use; safety not established.

**Adverse effects**
- **Common:** diarrhoea, nausea, anorexia, vomiting, upper abdominal pain (tolerance may develop), minor bleeding, mild-to-severe neutropenia, rash
- **Infrequent:** severe bleeding, hepatitis, mild increases in ALP, total cholesterol and triglycerides
- **Rare:** thrombocytopenia, aplastic anaemia, thrombotic thrombocytopenic purpura, Stevens–Johnson syndrome, erythema multiforme, exfoliative dermatitis, diarrhoea with severe colitis

**Dosage**
- Placement of coronary stent 250 mg twice daily with aspirin (100–300 mg once daily); initiate treatment on day of procedure and continue for 2–4 weeks.
- All other indications 250 mg twice daily.

**Patient counselling**
- Take with food to reduce stomach upset.
- Tell your doctor if you develop fevers, chills, sore throat, mouth ulcers, bleeding or bruising.

**Practice points**
- Use clopidogrel instead of ticlopidine if possible due to lower risk of severe adverse effects
- Risk of neutropenia is greatest in the first 12 weeks of treatment; obtain full blood count at baseline, then every 2 weeks for 3 months, then as indicated
- Stop ticlopidine if neutrophil count is <1.2x10⁹/L or platelet count is <80x10⁹/L; neutropenia is usually reversible on stopping ticlopidine

**Products**
- **TICLOPIDINE TABS 250 MG (PREVOC®, TICLID®, TICLOP®,)**

**TIROFIBAN**

**Mode of action**
Tirofiban is a non-peptide antagonist that prevents binding of fibrinogen to platelet, by occupying glycoprotein IIb/IIIa receptor, thereby blocking platelet aggregation.

**Indications**
Unstable angina and non-Q-wave MI in high risk patients

**Contraindications**
Severe uncontrolled hypertension (systolic BP >180 or diastolic BP >110 mm Hg), Active internal bleeding, Recent significant GI or genitourinary bleeding (within 6 weeks), Bleeding disorders, eg thrombocytopenia, haemophilia, von Willebrand's disease, History of intracranial disease (neoplasm, arteriovenous malformation, aneurysm), History of stroke (within a month for tirofiban and eptifibatide, within 2 years for abciximab) or any history of haemorrhagic stroke, Recent major surgery or trauma including epidural or spinal anaesthesia (within 6 weeks), History of vasculitis, Aortic dissection, Acute pericarditis INR >2.0

**Specific considerations**
Treatment with other drugs which can affect the clotting process: may increase the risk of bleeding; monitor closely (heparin and low dose aspirin are used therapeutically with abciximab, eptifibatide and tirofiban).
Renal impairment: Dose reduction is required.
Surgery: Stop treatment immediately if emergency coronary artery bypass graft surgery is required.
Pregnancy: Limited data available.
Breastfeeding: Limited data available.

**Adverse effects**
- **Common:** bleeding, thrombocytopenia
- **Rare:** allergic reactions, thrombocytopenic purpura

**Dosage**
- IV 0.4 microgram/kg/minute for 30 minutes, followed by 0.1 microgram/kg/minute for 48–108 hours.
- Renal impairment: Reduce dose by half when creatinine clearance <30 mL/minute.

**Practice points**
• give low dose aspirin and heparin infusion with tirofiban
• monitor PT, APTT, creatinine clearance, platelet count, haemoglobin and hematocrit before treatment; monitor haemoglobin, hematocrit and platelet count within 6 hours after start of treatment and at least once daily thereafter
• glycoprotein IIb/IIIa receptor inhibitors are used with heparin or LMWHs and low dose aspirin
• stop heparin, aspirin and glycoprotein IIb/IIIa receptor inhibitor if platelet count <100x10^9/L or drops 25% below baseline platelet count

**Products**

TIROFIBAN VIAL 0.25 MG/ML (AS HCL) (AGGRASTAT®)

### 02.10 MYOCARDIAL INFARCTION AND FIBRINOLYSIS

These notes give an overview of the initial and long-term management of myocardial infarction. The aims of management are to provide supportive care and pain relief, to promote revascularisation and to reduce mortality. Oxygen, diamorphine and nitrates provide initial support and pain relief; aspirin and percutaneous coronary intervention or thrombolytics promote revascularisation; long-term use of aspirin, beta-blockers, ACE inhibitors and statins help to reduce mortality further.

**Initial management**

Oxygen is administered unless the patient has severe chronic obstructive pulmonary disease.

The pain (and anxiety) of myocardial infarction is managed with slow intravenous injection of diamorphine; an antiemetic such as metoclopramide (or, if left ventricular function is not compromised, cyclizine) by intravenous injection should also be given.

Aspirin (chewed or dispersed in water) is given for its antiplatelet effect; a dose of 150–300 mg is suitable. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient.

Patency of the occluded artery can be restored by percutaneous coronary intervention or by giving a thrombolytic drug, unless contra-indicated. Alteplase, reteplase and streptokinase need to be given within 12 hours of a myocardial infarction, ideally within 1 hour; use after 12 hours requires specialist advice. Tenecteplase should be given within 6 hours of a myocardial infarction. Antibodies to streptokinase appear after 4 days and it should not therefore be used again after this time. Heparin is used as adjunctive therapy with alteplase, reteplase, and tenecteplase to prevent re-thrombosis; heparin treatment should be continued for at least 24 hours.

Nitrates are used to relieve ischaemic pain. If sublingual glyceryl trinitrate is not effective, intravenous glyceryl trinitrate or isosorbide dinitrate is given.

Early intravenous administration of some beta-blockers has been shown to be of benefit and patients without contra-indications should receive atenolol by intravenous injection at a dose of 5 mg over 5 minutes, and the dose repeated once after 10–15 minutes; metoprolol by intravenous injection is an alternative.

ACE inhibitors are also of benefit to patients who have no contra-indications; in hypertensive and normotensive patients treatment with an ACE inhibitor can be started within 24 hours of the myocardial infarction and continued for at least 5–6 weeks (see below for long-term treatment).

All patients should be closely monitored for hyperglycaemia; those with diabetes or raised blood-glucose concentration should receive insulin.

**Long-term management**

Long-term management involves the use of several drugs which should ideally be started before the patient is discharged from hospital.

Aspirin should be given to all patients, unless contra-indicated, at a dose of 75 mg daily. Warfarin (with or without aspirin) may confer greater benefit than aspirin alone, but the risk of bleeding is increased.

Beta-blockers should be given to all patients in whom they are not contra-indicated and continued for at least 2–3 years. Acebutolol, metoprolol, propranolol and timolol are suitable; for patients with left ventricular dysfunction, carvedilol, bisoprolol or long-acting metoprolol may be appropriate.

Verapamil may be useful if a beta-blocker cannot be used; however, other calcium-channel blockers have no place in routine long-term management after a myocardial infarction.

An ACE inhibitor should be considered for all patients, especially those with evidence of left ventricular dysfunction.

If an ACE inhibitor cannot be used, an angiotensin-II receptor antagonist may be used for patients with heart failure. A relatively high dose of either the ACE inhibitor or angiotensin-II receptor antagonist may be required to produce benefit.

Nitrates are used for patients with angina.

Statins are beneficial in preventing recurrent coronary events.
02.10.01 Fibrinolytics

Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

The value of thrombolytic drugs for the treatment of myocardial infarction has been established. Streptokinase has been shown to reduce mortality. Reteplace and tenecteplase are also licensed for acute myocardial infarction; they are given by intravenous injection (tenecteplase is given as a bolus injection). Thrombolytic drugs are indicated for any patient with acute myocardial infarction for whom the benefit is likely to outweigh the risk of treatment. Trials have shown that the benefit is greatest in those with ECG

STREPTOKINASE

Mode of action
Converts plasminogen to plasmin, which then catalyses the breakdown of fibrin.

Indications
Acute MI
Acute massive thromboembolism in patients who are haemodynamically unstable
Peripheral arterial thromboembolism
Thrombosed haemodialysis shunts

Contraindications
Active internal bleeding, Recent (<1 year) stroke, Recent (<1 month) major surgery or trauma, Intracranial neoplasm
Prior intracranial haemorrhage, Bleeding disorder, Non-compressible vascular puncture (including lumbar puncture), Severe uncontrolled hypertension (systolic BP >200 mm Hg or diastolic BP >110 mm Hg), Bacterial endocarditis, pericarditis, Haemorrhagic retinopathy, Suspicion of left heart thrombus (eg mitral stenosis with AF). Recent(<10 days) prolonged or traumatic cardiopulmonary resuscitation.

Specific considerations
Streptokinase treatment or severe streptococcal infection (eg acute rheumatic fever, glomerulonephritis) in previous 12 months or more: anti-streptokinase antibodies are likely to be present; efficacy of streptokinase is likely to be reduced.
Recent GI bleeding, parturition, organ biopsy or cavitating tuberculosis: increased risk of adverse effects; use with caution.
Treatment with drugs which can affect the clotting process, eg oral anticoagulants, glycoprotein IIb/IIIa receptor inhibitors: increases the risk of bleeding; monitor combinations closely. Use low dose aspirin where indicated.
Hepatic impairment: Avoid use in severe impairment; increased risk of bleeding.
Pregnancy: Only minimal amounts of streptokinase cross the placenta; streptokinase-specific antibodies are found in fetal blood. Avoid use unless expected benefit outweighs risk of maternal and fetal haemorrhage. ADEC category C.
Breastfeeding: No data available.

Adverse effects
Common: bleeding, including bleeding at injection sites, intracerebral bleeding, internal bleeding (eg GI, genitourinary)
Infrequent: allergic reactions including fever, chills, rash, nausea, headache, bronchospasm, anaphylaxis, vasculitis, nephritis, hypotension
Rare: cholesterol embolism

Dosage
Acute MI
IV infusion, 1 500 000 units over 30–60 minutes.
Deep venous thrombosis, pulmonary or peripheral arterial thromboembolism
IV, 250 000 units infused over 30 minutes, then 100 000 units/hour for 24–72 hours.
Intra-arterial, 5000 units/hour infused locally; duration of infusion determined by response.
Thrombosed haemodialysis shunt
Instil 250 000 units in 2 mL sodium chloride 0.9% into affected limb of cannula and clamp off for 2–4 hours.

Practice points
• stop heparin before giving streptokinase; check APTT (which should be less than twice the normal control value before beginning thrombolytic treatment and before reinstituting heparin)
• give patients a record of streptokinase use so this information is available in the event of subsequent use
• avoid IM injections and other invasive procedures during thrombolytic treatment
• hypotension may be prevented by fluid loading, eg 500–1500 mL 0.9% sodium chloride before or during treatment, provided there are no contraindications (acute pulmonary oedema, renal failure); if hypotension
occurs it usually responds to slowing or stopping infusion of thrombolytic; IV fluids and, rarely, inotropes may be required

- in case of severe bleeding not controlled by local pressure, stop infusion of thrombolytic; fibrinogen, platelets, coagulation factors, tranexamic acid may be useful (or protamine if heparin has been used)

**Products**

**STREPTOKINASE VIAL 1,500,000 IU/VIAL (STOKINASE®, STREPTASE®)**

**TENECTEPLASE**

**Mode of action**
Same as Sterptokinase.

**Indications**
Same as Sterptokinase

**Contraindications**
Same as Sterptokinase

**Specific considerations**
Same as Sterptokinase

**Adverse effects**
Same as Sterptokinase

**Dosage**
Give with weight-adjusted heparin

- <60 kg, IV 30 mg (6000 units).
- 60–70 kg, IV 35 mg (7000 units).
- 70–80 kg, IV 40 mg (8000 units).
- 80–90 kg, IV 45 mg (9000 units).
- >90 kg, IV 50 mg (10 000 units).

**Practice points**
- give aspirin in antiplatelet dose at least until discharge
- avoid IM injections and other invasive procedures during thrombolytic treatment
- in case of severe bleeding not controlled by local pressure, stop infusion of thrombolytic; fibrinogen, platelets, coagulation factors, tranexamic acid may be useful (or protamine if heparin has been used)

**Products**

**TENECTEPLASE PLASMINOGEN ACTIVATOR VIAL+PFS SOLVENT 10,000 IU/VIAL (METALYSE®)**

**02.11 LIPID REGULATING DRUGS (DYSLIPIDAEMIA)**

**Rationale for drug use**
Reduce progression of atherosclerosis, improve survival and reduce risk of MI and stroke in patients with established cardiovascular disease.
Reduce premature cardiovascular morbidity and mortality in people at high risk of cardiovascular events.
Prevent pancreatitis due to hypertriglyceridaemia.

**Before starting treatment**
Measure fasting plasma lipid profile.
Consider cardiovascular status and risk factors.
Treat secondary causes of dyslipidaemia, eg obesity, diabetes, hypothyroidism, obstructive liver disease, nephrotic syndrome, excess alcohol intake.
Manage other modifiable cardiovascular risk factors, eg hypertension, and encourage healthy lifestyle changes, eg stopping smoking, reducing weight, modifying diet and increasing physical activity.
Institute other secondary prevention strategies, eg aspirin for established coronary artery disease.
Consider referral to dietitian.

**Important Note :**
Rhabdomyolysis associated with lipid-regulating drugs such as the fibrates and statins appears to be rare (approx. 1 case in every 100 000 treatment years) but may be increased in those with renal impairment and possibly in those with hypothyroidism. Concomitant treatment with drugs that increase plasma-statin concentration increase the risk of muscle toxicity; concomitant treatment with a fibrate and a statin may also be associated with an increased risk of serious muscle toxicity.

**When to start treatment**
Large clinical trials have shown that people at highest risk of cardiovascular events (eg those with pre-existing
ischaemic heart disease) will derive the greatest absolute benefit from lipid lowering drugs. Target treatment with drugs to those at greatest risk, rather than considering cholesterol and lipid concentrations alone.

Consider drug treatment in addition to diet and lifestyle changes for any patient with cardiovascular, cerebrovascular or peripheral vascular disease, diabetes or multiple cardiovascular risk factors and baseline cholesterol concentration >3.5 mmol/L (this differs from PBS criteria).

**Drug choice**
statins are drugs of choice for treating hypercholesterolaemia and fibrates for treating hypertriglyceridaemia, statins and fibrates can be used, either alone or together to treat mixed hyperlipidaemia.

**Hypercholesterolaemia**

**Statins**
Most effective LDL lowering agents (typical reduction 30–50%); well tolerated. In patients at high risk of cardiovascular disease (with or without coronary heart disease) statins reduce the risk of MI, stroke, revascularisation procedures and mortality.

**Bile acid binding resins**
Useful for isolated hypercholesterolaemia (typically reduce LDL by 15–25%). They may worsen hypertriglyceridaemia if triglyceride is >3 mmol/L. Poorly tolerated, especially in high doses, but useful in combination treatment when used in low dosage. Cholestyramine reduced the risk of non-fatal MI and death due to coronary heart disease in men without heart disease and total cholesterol >6.8 mmol/L.

**Nicotinic acid**
Has good LDL and triglyceride lowering effects and produces a marked increase in HDL (typically reduces LDL by 15–30%, triglycerides by 25–40% and increases HDL by 20–35%). Use is limited by adverse effects.

**Ezetimibe**
Reduces LDL by about 18% and is well tolerated. Further studies are needed to demonstrate its safety and effect on clinical outcomes, when used alone and with other lipid lowering drugs.

**Fibrates**
May be considered if drugs listed above are not tolerated. Gemfibrozil generally reduces LDL by 5–15% and reductions of up to 25% are reported for fenofibrate. Gemfibrozil was shown to reduce risk of non-fatal MI and death due to coronary heart disease in men without cardiovascular disease and elevated total cholesterol; greatest benefit when HDL <1 mmol/L and triglyceride >2.3 mmol/L, and in those with metabolic syndrome (insulin resistance, hypertension, overweight).

**Hypertriglyceridaemia and low HDL**
Consider secondary causes, eg diabetes, insulin resistance. Low-fat diet, weight loss, limiting alcohol intake, and increasing physical activity are particularly effective for reducing triglyceride and increasing HDL.

Although raised triglyceride is a risk factor for coronary artery disease, particularly in women, conclusive evidence that reducing it with drugs improves cardiovascular outcome is lacking (no clinical trial primarily targeting triglyceride has been conducted).

**Fibrates**
Markedly reduce triglycerides (40–80%) and increase HDL (10–30%); in pure hypertriglyceridaemia, LDL may increase. First choice for hypertriglyceridaemia as have similar efficacy to nicotinic acid but are better tolerated. Gemfibrozil reduced the risk of non-fatal MI and coronary death in men with coronary heart disease, low LDL (<3.6 mmol/L), HDL <1 mmol/L and triglyceride <3.4 mmol/L.

**Nicotinic acid**
Has similar efficacy to fibrates but poorly tolerated.

**Fish oils**
Reduce plasma triglyceride concentration when taken daily in doses containing 2–5 g omega-3 fatty acids. The content of these fatty acids varies between products, so dosage should be calculated for each one. A daily dose of >6 capsules is required to reduce triglyceride concentrations for brands where a 1 g capsule contains 300 mg omega-3 fatty acids (180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid).

Fish oil supplements appear to be safe with few adverse effects; high doses may increase bleeding time. They may be useful if fibrates and nicotinic acid are not tolerated. Eating at least 2 fish meals each week is recommended for the general population.

**Mixed hyperlipidaemia**
Initial choice is guided by predominant disorder:
- raised cholesterol, start with a statin
• raised triglyceride, generally choose a fibrate. However, consider a statin first if the patient has cardiovascular disease as there are more data for their efficacy.

Nicotinic acid lowers cholesterol and triglyceride concentrations, but is often poorly tolerated.

**Combination treatment**

Combination treatment may be appropriate if a single agent is inadequate (e.g., adding fish oil to lower triglyceride, or adding ezetimibe or a bile acid binding resin to reduce cholesterol concentration). It is difficult to assess the potential benefit versus harm for various combination treatments, as there are few studies with clinical outcomes. Combined use of a statin and a fibrate is often effective in improving dyslipidaemia, but may increase the risk of serious adverse effects; seek specialist advice.

**Special cases**

Pregnancy: Lowering cholesterol or triglyceride with drugs or diet is usually inappropriate, except for massive increase in triglyceride (increases risk of pancreatitis); seek specialist advice. Physiological hyperlipidaemia of pregnancy does not require treatment.

Children: Seek specialist advice. Treatment is usually dietary, and drug treatment postponed until adulthood.

**Unanswered questions**

- at what point is the benefit of lowering cholesterol concentration outweighed by harm or expense?
- as studies have shown that lowering LDL to <2 mmol/L is beneficial in high risk patients whose LDL is already low, do we aim for specific target concentrations (according to risk of cardiovascular disease) or use fixed dose regimens?
- if combination treatments are needed to reach target, how do their risks and benefits compare with those of high dose statins alone?
- are benefits of statins due only to cholesterol lowering (if they have other beneficial properties, are these class effects or do they differ between the statins)?
- what is the evidence of safety and efficacy (clinical outcomes) for ezetimibe, complementary and dietary treatments, e.g., plant sterols, psyllium fibre?

**Practice points**

- encourage adherence to diet and lifestyle changes at each review
- measure lipids every 4–6 weeks during dose titration (maximum effect of a given dose of lipid regulating agent is achieved after at least 4 weeks, longer for gemfibrozil); then measure lipids every 6–12 months during maintenance
- if response to a single agent is inadequate, first question compliance and then consider using an alternative agent or an additional drug

**02.11.01 Fibrates group**

**BEZAFIBRATE**

**Mode of action**

Activate peroxisome proliferator-activated nuclear receptors and modulate lipoprotein synthesis and catabolism. They reduce plasma triglyceride, moderately increase HDL and have a variable effect on LDL concentrations.

**Indications**

Severe hypertriglyceridaemia with risk of pancreatitis (adjunct to diet)
Mixed hyperlipidaemia and dyslipidaemia associated with diabetes (adjunct to diet)
Hypercholesterolaemia, second line (adjunct to diet)

**Contra-indications**

Primary biliary cirrhosis, gallstones or gall bladder disease
Severe renal impairment
Hepatic impairment

**Specific considerations**

Children: Seek specialist advice.
Pregnancy: Avoid use of lipid lowering drugs, ADEC category B3.
Breastfeeding: No data available

**Adverse effects**

Common: GI disturbances (e.g., dyspepsia, abdominal pain)
Rare: cholestatic jaundice, gallstones, anaemia, leucopenia, myopathy, rhabdomyolysis, hypersensitivity reactions (e.g., angioedema, anaphylaxis, exfoliative dermatitis)
Patient counselling
Tell your doctor if muscle pain, tenderness or weakness occur.

Practice points
- measure full blood count and liver function before starting and during treatment

Products
BEZAFIBRATE TABS 200 MG (BEZALIP®, ZAFIBRAL®)

ETOFIBRATE
Same as Bezafibrate

Products
ETOFIBRATE CAPS 500 MG (LIPO-MERZ®)

GEMFIBROZIL

Mode of action
Activate peroxisome proliferator-activated nuclear receptors and modulate lipoprotein synthesis and catabolism. They reduce plasma triglyceride, moderately increase HDL and have a variable effect on LDL concentrations.

Indications
Severe hypertriglyceridaemia with risk of pancreatitis (adjunct to diet)
Mixed hyperlipidaemia and dyslipidaemia associated with diabetes (adjunct to diet)
Hypercholesterolaemia, second line (adjunct to diet)

Contraindications
Allergy to gemfibrozil, Treatment with repaglinide, Primary biliary cirrhosis, gallstones or gall bladder disease, Severe renal impairment, Hepatic impairment

Specific considerations
Children: Seek specialist advice.
Pregnancy: Avoid use of lipid lowering drugs, ADEC category B3.
Breastfeeding: No data available; contact specialised information service.

Adverse effects
Common: dry mouth, headache, myalgia
GI disturbances (eg dyspepsia, abdominal pain)
Infrequent: AF, appendicitis
Rare: increased transaminase concentrations, impotence, reduced libido, depression, paraesthesia, peripheral neuritis, dizziness, taste disturbance, urticaria, cholestatic jaundice, gallstones, anaemia, leucopenia, myopathy, rhabdomyolysis, hypersensitivity reactions (eg angioedema, anaphylaxis, exfoliative dermatitis)

Comparative information
Gemfibrozil has been shown to reduce the incidence of major cardiovascular events in:
- men with cardiovascular disease and HDL <1 mmol/L and low LDL (<3.6 mmol/L)
- men without cardiovascular disease with elevated total cholesterol; greatest benefit when HDL <1 mmol/L and triglyceride >2.3 mmol/L, and in those with metabolic syndrome (insulin resistance, hypertension, overweight).

Dosage
600 mg twice a day.

Administration instructions
This medicine is absorbed best if you take it half an hour before food. However, if it upsets your stomach, take it with meals.

Patient counselling
Seek medical advice if muscle pain, tenderness or weakness occur.

Practice points
- consider gemfibrozil for isolated hypercholesterolaemia only if more potent agents (eg statin, ezetimibe, resin or nicotinic acid) are not tolerated
- measure full blood count and liver function before starting and during treatment
EZETIMIBE
Experience with this drug is limited; previously unreported adverse effects or drug interactions may occur.

Mode of action
Reduces absorption of dietary and biliary cholesterol by inhibiting its transport across the intestinal wall. This leads to an increased demand for cholesterol, an increase in LDL uptake and its removal from the plasma.

Indications
Hypercholesterolaemia (adjunct to diet)
Homozygous sitosterolaemia (phytosterolaemia), adjunct to diet
Combination with simvastatin
Hypercholesterolaemia when a statin alone is inadequate (adjunct to diet)

Contraindications
Allergy to ezetimibe

Specific considerations
Hepatic impairment: Manufacturer recommends avoiding use in moderate and severe impairment (Child–Pugh >6).
Children: There is limited experience in children. Children >10 years with homozygous familial hypercholesterolaemia and sitosterolaemia have been given the same dose as adults. Seek specialist advice.
Pregnancy: No human data, avoid use. ADEC category B3.
Breastfeeding: No human data

Adverse effects
Common: headache, diarrhoea
Infrequent: myalgia, raised ALT/AST >3 times upper limit of normal
Rare: allergic reactions (angioedema, rash), myopathy, raised creatine kinase

Dosage
10 mg once daily.

Patient counselling
Tell your doctor if you have any muscle pain, tenderness or weakness.

Practice points
- there is no evidence that this drug reduces clinical events; only short term studies (8–14 weeks) are available, showing that it reduces LDL concentrations and is well tolerated
- until further studies (long term, clinical outcomes) are available it should not be used in preference to other agents that have such data to support their use

Use with other lipid lowering drugs
- like bile acid resins it can be added to treatment with a statin to:
  - increase the LDL lowering effect of the statin (by up to 20%)
  - enable greater lipid lowering efficacy from lower doses of statin (especially in those who cannot tolerate high doses)
- further data are needed to clarify risk/benefit when used with other lipid lowering agents; limited data suggest that ezetimibe may increase the incidence of adverse effects when used with a statin:
  - incidence ALT/AST >3 times upper limit of normal increased from 0.4% for statin alone to 1.2%
  - incidence of myalgia increased from 2.4% for statin alone to 3.2%

Products
EZETIMIBE TABS 10 MG (EZETROL®)

02.11.02 Statins group

ATORVASTATIN

Mode of action
Competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (a rate-limiting enzyme in cholesterol synthesis). Increase hepatic cholesterol uptake from blood, reduce concentrations of total cholesterol, LDL and triglyceride (modest), and produce a small increase in HDL concentrations.

Indications
Marketed: Hypercholesterolaemia (adjunct to diet)
Hypertensive patients with other risk factors for heart disease (eg age >55 years, diabetes, stroke, smoking,
peripheral vascular disease
Accepted: Mixed hyperlipidaemia (adjunct to diet)

Specific considerations
Women of child-bearing potential: use adequate contraception; warn of potential hazard to fetus.
Severe intercurrent illness (infection, trauma, metabolic disorder): increases risk of myopathy, rhabdomyolysis and renal failure; consider withholding statin during illness (see also Practice points).
Previous myopathy with lipid lowering agent: increases risk of myopathy with statin.
Renal impairment: Increases risk of myopathy and rhabdomyolysis; start at low dose and monitor renal function and creatine kinase regularly.
Hepatic impairment: Chronic liver disease increases concentration of atorvastatin which may increase risk of adverse effects; seek specialist advice.
Monitor transaminase concentrations before, and at intervals during, treatment.
Surgery: Consider withholding statin a few days before major surgery (unless symptoms of an acute coronary syndrome are present, patient may be at increased risk of myopathy, rhabdomyolysis and renal failure.
Elderly: Risk of myopathy is higher especially if frail, age >80 years or multiple diseases present; use cautiously and start at low dosage.
Children: Seek specialist advice. The long term risks and benefits from treating children with statins, with the aim of reducing disease in adulthood, are unknown.
Pregnancy: Contraindicated. Use during first trimester has been associated with fetal malformation; ADEC category D.
Breastfeeding: No data available; contact specialised information service.

Adverse effects
Common: myalgia, mild transient GI symptoms, headache, insomnia, dizziness, elevated transaminase concentrations
Rare: myopathy, rhabdomyolysis, renal failure, hepatitis, liver failure, alopecia, paraesthesia, peripheral neuropathy, impotence, nightmares, gynaecomastia, hypersensitivity, anaphylaxis, angioedema, toxic epidermal necrolysis
Myopathy, rhabdomyolysis: Risk of myopathy (with or without creatine kinase elevation) and rhabdomyolysis are dose-related. Risk is also increased by illness, and certain drug interactions.

Transaminase concentrations
Elevated transaminases occur in 0.5–2% of patients treated with statins; it is dose-dependent, generally responds to a reduction in dosage and does not usually recur on rechallenge or use of another statin.

Dosage
Initially 10 mg daily; adjust after 4 weeks if necessary; maximum dose 80 mg daily.

Patient counselling
Avoid grapefruit juice as it may increase the amount of atorvastatin in your bloodstream and could increase the chances of side effects occurring.
Take once daily, preferably in the evening, because morning doses are slightly less effective. (Atorvastatin can be taken at any time, as it is not affected like this.)
Seek medical advice promptly if you experience muscle pain, tenderness or weakness.

Practice points
- avoid stopping statin if symptoms of an acute coronary syndrome are present because stopping is associated with an increased rate of cardiac events (especially in the first week after stopping)
- more than 80% of the LDL lowering effect of a statin is achieved with 50% of maximum dose (eg simvastatin 40 mg); adding a bile acid binding resin (in low dosage), ezetimibe or a sterol margarine at this point can be much more effective in reducing LDL than increasing the dose of statin (although effect on clinical outcomes of such combinations, compared to high dose statin alone, are unknown)
- in mixed hyperlipidaemia, a statin can be used with a more potent triglyceride lowering drug, eg fish oil or gemfibrozil if necessary

Monitoring
- monitor transaminase and creatine kinase (CK) at baseline, repeat during treatment if indicated clinically; monitoring every 6–12 months is recommended for children taking pravastatin
- stop statin if:
  - transaminase concentrations are persistently elevated to >3 times the upper limit of normal
  - CK concentration is >10 times the upper limit of normal
  - there is persistent unexplained muscle pain (even if CK is normal)
• treatment may be resumed after at least 4 weeks if myopathy/myositis was mild and CK concentration, if raised, has returned to normal. Consider:
  o whether a precipitant (eg trauma, surgery) or a drug interaction contributed to this adverse effect (see Statins)
  o using a lower dose (as these adverse effects are dose-related)
  o using an alternative statin (although there are no data comparing risk between agents)
• if the problem recurs on rechallenge, stop statins permanently

Products
ATORVASTATIN TABS 20 MG (AS CALCIUM TRIHYDRATE) (ADITOR®, ATROVAST®, LIPITOR®, LIPODAR®, TORVACOL®, VASTOR®)

FLUVASTATIN
Mode of action
Same as Atorvastatin
Indications
Hypercholesterolaemia (adjunct to diet)
Coronary disease after successful percutaneous coronary intervention
Mixed hyperlipidaemia (adjunct to diet)
High risk of coronary heart disease, with or without hypercholesterolaemia
Specific considerations
Adverse effects
Same as Atorvastatin
Dosage
Initially 20 mg once a day; adjust after 4 weeks if necessary. Usual range, 20–40 mg once a day. Maximum, 40 mg twice a day.
Coronary disease: 40 mg twice daily.
Patient counselling
Take once daily, preferably in the evening, because morning doses are slightly less effective. Seek medical advice promptly if you experience muscle pain, tenderness or weakness.
Practice points
• abdominal pain and dyspepsia are more common with the maximum dose
• avoid stopping statin if there are symptoms of an acute coronary syndrome because stopping is associated with an increased rate of cardiac events (especially in the first week after stopping)
• more than 80% of the LDL lowering effect of a statin is achieved with 50% of maximum dose (eg simvastatin 40 mg); adding a bile acid binding resin (in low dosage), ezetimibe or a sterol margarine at this point can be much more effective in reducing LDL than increasing the dose of statin (although effect on clinical outcomes of such combinations, compared to high dose statin alone, are unknown)
• in mixed hyperlipidaemia, a statin can be used with a more potent triglyceride lowering drug, eg fish oil or emfibrozil if necessary, see Dyslipidaemia

Products
FLUVASTATIN CAPS 40 MG (LESCOL®)
FLUVASTATIN TABS 80 MG (LESCOL XL®)

PRAVASTATIN
Mode of action
Same as Atorvastatin
Indications
Marketed
Hypercholesterolaemia (adjunct to diet)
Post MI (including combination with aspirin)
Unstable angina (includes combination with aspirin)
High risk of coronary heart disease, with or without hypercholesterolaemia
Heterozygous familial hypercholesterolaemia (FH) in children (8 years and older), adjunct to diet and exercise
Accepted: Mixed hyperlipidaemia (adjunct to diet)
Adverse effects
Same as Atorvastatin

**Dosage**

**Adult**
Initially 10–20 mg once daily; adjust at intervals of 4 weeks if necessary, up to 80 mg daily.
Renal impairment and elderly: Initially 10 mg once daily; adjust as above.
Unstable angina and post MI: 40 mg once daily. adjust as above.
Child: 8–13 years, 20 mg once daily, 14–18 years, 40 mg once daily.

**Patient counselling**
Take once daily, preferably in the evening, because morning doses are slightly less effective. (Atorvastatin can be taken at any time.)
Seek medical advice promptly if you experience muscle pain, tenderness or weakness.

**Practice points**
Same as Atorvastatin

**Monitoring**
- monitor transaminase and creatine kinase at baseline, repeat during treatment if indicated clinically; monitoring every 6–12 months is recommended for children taking pravastatin
- stop statin if:
  - transaminase concentrations are persistently elevated to >3 times the upper limit of normal
  - creatine kinase concentration is >10 times the upper limit of normal
  - the patient complains of persistent unexplained muscle pain (even if creatine kinase is normal)
- treatment may be resumed after at least 4 weeks if myopathy/myositis was mild and CK concentration, if raised, has returned to normal. Consider:
  - whether a precipitant (eg trauma, surgery) or a drug interaction contributed to this adverse effect (see Statins)
  - using a lower dose (as these adverse effects are dose-related)
  - using an alternative statin (although there are no data comparing risk between agents)
- if the problem recurs on rechallenge, stop statins permanently

**Products**
PRAVASTATIN TABS 40 MG (LIPOSTAT®)

**SIMVASTATIN**

**Mode of action**
Same as Atorvastatin

**Indications**
Marketed
Hypercholesterolaemia (adjunct to diet)
Patients at high risk of coronary heart disease, with or without hypercholesterolaemia, eg diabetes, peripheral vascular disease, coronary or cerebrovascular disease
Combination with ezetimibe
Hypercholesterolaemia (adjunct to diet), when treatment with a statin alone is insufficient
Accepted: Mixed hyperlipidaemia (adjunct to diet)

**Adverse effects**
Same as Atorvastatin

**Dosage**
Existing or high risk of coronary heart disease: Usual dose, 40 mg once a day.
Other indications: Initially 10–20 mg once a day; adjust at intervals of 4 weeks if necessary.
Maximum dose: 80 mg daily.

**Patient counselling**
Avoid grapefruit juice as it may increase the amount of simvastatin in your bloodstream and could increase the chances of side effects occurring.
Take once daily, preferably in the evening, because morning doses are slightly less effective. (Atorvastatin can be taken at any time, as it is not affected like this.)
Seek medical advice promptly if you have any muscle pain, tenderness or weakness.

**Practice points**
- myopathy is more common with the maximum dose, and increasing dose from 40 mg is only likely to reduce LDL by an additional 7%
Combination with ezetimibe

- do not start treatment of dyslipidaemia with simvastatin and ezetimibe combination tablets
- combination with ezetimibe gives further reduction in LDL concentrations (of about 20%) which may be useful when:
  - high doses of simvastatin are needed but cannot be tolerated
  - simvastatin treatment is inadequate despite maximum dosage
- further data are needed to clarify risk/benefit of this combination as limited data suggest that ezetimibe may increase the incidence of adverse effects:
  - incidence ALT/AST >3 times upper limit of normal increased from 0.4% for statin alone to 1.2%
  - incidence of myalgia increased from 2.4% for statin alone to 3.2%
- measure baseline ALT and AST when starting simvastatin and ezetimibe combination
- avoid stopping statin if there are symptoms of an acute coronary syndrome because stopping is associated with an increased rate of cardiac events (especially in the first week after stopping)
- more than 80% of the LDL lowering effect of a statin is achieved with 50% of maximum dose (e.g., simvastatin 40 mg); adding a bile acid binding resin (in low dosage), ezetimibe, or a sterol margarine at this point can be much more effective in reducing LDL than increasing the dose of statin (although effect on clinical outcomes of such combinations, compared to high dose statin alone, are unknown)
- in mixed hyperlipidaemia, a statin can be used with a more potent triglyceride lowering drug, e.g., fish oil or gemfibrozil if necessary

Monitoring

- monitor transaminase and creatine kinase (CK) at baseline, repeat during treatment if indicated clinically; monitoring every 6–12 months is recommended for children taking pravastatin
- stop statin if:
  - transaminase concentrations are persistently elevated to >3 times the upper limit of normal
  - CK concentration is >10 times the upper limit of normal
  - there is persistent unexplained muscle pain (even if CK is normal)
- treatment may be resumed after at least 4 weeks if myopathy/myositis was mild and CK concentration, if raised, has returned to normal. Consider:
  - whether a precipitant (e.g., trauma, surgery) or a drug interaction contributed to this adverse effect (see Statins)
  - using a lower dose (as these adverse effects are dose-related)
  - using an alternative statin (although there are no data comparing risk between agents)
- if the problem recurs on rechallenge, stop statins permanently

Products

SIMVASTATIN TABS 20 MG (CHOLASTIN®, LIPOMID®, SIMVATIN®, SIMVER®, SIVACOR®, ZOCOR®)
### Table 02-01 Comparative information for sympathomimetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Receptor activity</th>
<th>Physiological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alpha</td>
<td>Beta&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>dobutamine</td>
<td>low</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>dopamine</td>
<td>intermediate</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>adrenaline</td>
<td>low</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>high</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>isoprenaline</td>
<td></td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>noradrenaline</td>
<td></td>
<td>++++</td>
<td>+</td>
</tr>
</tbody>
</table>

VD = vasodilation; VC = vasoconstriction; INT = positive inotropism; CHT = positive chronotropism

### Table 02-02 Comparative information for nitrates

<table>
<thead>
<tr>
<th>Oral bioavailability&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Route</th>
<th>Onset of effect</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyceryl trinitrate</td>
<td>sublingual aerosol&lt;sup&gt;2&lt;/sup&gt; or tablet</td>
<td>&lt;5 minutes</td>
<td>&lt;1 hour</td>
</tr>
<tr>
<td>poor</td>
<td>patch</td>
<td>30–60 minutes</td>
<td>prolonged&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>infusion</td>
<td>&lt;10 minutes</td>
<td>variable&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>oral tablet</td>
<td>15–40 minutes</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>20–25%</td>
<td>sublingual tablet</td>
<td>&lt;10 minutes</td>
<td>1–2 hours</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>controlled release tablet</td>
<td>1–2 hours</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

1 when swallowed
2 more stable than sublingual tablet; for patients with infrequent symptoms
3 prolonged duration of effect because of continued absorption
4 duration of effect depends on duration of infusion
Table 02-03 Factors influencing prognosis in hypertension

<table>
<thead>
<tr>
<th>Risk factors for cardiovascular diseases</th>
<th>Target organ disease</th>
<th>Associated clinical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• level of BP</td>
<td>• left ventricular hypertrophy</td>
<td>• diabetes</td>
</tr>
<tr>
<td>• men &gt;55 years</td>
<td>• microalbuminuria and/or proteinuria and/or glomerular filtration rate &lt;60 mL/minute</td>
<td>• cerebrovascular disease</td>
</tr>
<tr>
<td>• women &gt;65 years</td>
<td>• ultrasound or angiographic evidence of atherosclerotic disease</td>
<td>• coronary heart disease or heart failure</td>
</tr>
<tr>
<td>• smoking</td>
<td>• hypertensive retinopathy (grade II or more)</td>
<td>• chronic kidney disease (diabetic nephropathy, glomerulonephritis, hypertensive renovascular disease)</td>
</tr>
<tr>
<td>• dyslipidaemia</td>
<td></td>
<td>• aortic disease (dissecting aneurysm, fusiform aortic aneurysm)</td>
</tr>
<tr>
<td>• family history of cardiovascular disease onset &lt;60 years</td>
<td></td>
<td>• peripheral arterial disease</td>
</tr>
<tr>
<td>• excessive alcohol intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sedentary lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Aboriginal, Torres Strait or Pacific Islanders, Maoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• lower socioeconomic groups</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from: Hypertension management guide for doctors, 2004, National Heart Foundation of Australia.

Table 02-04 Coexisting conditions and antihypertensive choice

<table>
<thead>
<tr>
<th>Coexisting condition</th>
<th>Drugs with favourable effect</th>
<th>Drugs with unfavourable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes with microalbuminuria</td>
<td>ACE inhibitors, angiotensin II antagonists</td>
<td>beta-blockers*</td>
</tr>
<tr>
<td>heart failure</td>
<td>ACE inhibitors, beta-blockers (carvedilol, controlled release metoprolol, bisoprolol), thiazide diuretics, angiotensin II antagonists</td>
<td>beta-blockers (except oxprenolol, pindolol), ACE inhibitors (left ventricular dysfunction)</td>
</tr>
<tr>
<td>post MI</td>
<td>beta-blockers (except oxprenolol, pindolol), calcium channel blockers</td>
<td>beta-blockers, calcium channel blockers (except dihydropyridines)</td>
</tr>
<tr>
<td>angina</td>
<td>beta-blockers*</td>
<td>verapamil, diltiazem, selective alpha-blockers</td>
</tr>
<tr>
<td>Coexisting condition</td>
<td>Drugs with unfavourable effect</td>
<td>diuretics</td>
</tr>
<tr>
<td>asthma, COPD</td>
<td>beta-blockers*</td>
<td>ACE inhibitors, angiotensin II antagonists</td>
</tr>
<tr>
<td>bradycardia, second or third degree atrioventricular block</td>
<td>beta-blockers, calcium channel blockers (except dihydropyridines)</td>
<td></td>
</tr>
<tr>
<td>heart failure</td>
<td>verapamil, diltiazem, selective alpha-blockers</td>
<td></td>
</tr>
<tr>
<td>gout</td>
<td>diuretics</td>
<td>ACE inhibitors, angiotensin II antagonists</td>
</tr>
<tr>
<td>renovascular disease, pregnancy</td>
<td>beta-blockers</td>
<td>beta-blockers</td>
</tr>
<tr>
<td>severe peripheral vascular disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*cardioselective beta-blockers (eg atenolol, metoprolol) may be used cautiously in mild-to-moderate reactive airways diseases
**Table 02-05 Hypertension: BP targets for adults**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Target BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>proteinuria &gt;1 g/day</td>
<td>&lt;125/75 mm Hg</td>
</tr>
<tr>
<td>&lt;65 years (unless covered above) or</td>
<td></td>
</tr>
<tr>
<td>diabetes or</td>
<td></td>
</tr>
<tr>
<td>renal impairment or</td>
<td>&lt;130/85 mm Hg</td>
</tr>
<tr>
<td>proteinuria 0.25–1 g/day</td>
<td></td>
</tr>
<tr>
<td>65 years and over (unless covered above)</td>
<td>&lt;140/90 mm Hg</td>
</tr>
</tbody>
</table>

**Table 02-06 Comparative information for beta-blockers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptors antagonised</th>
<th>ISA Lipid solubility</th>
<th>Main route of elimination</th>
<th>Half-life (hours)</th>
<th>Number of daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol</td>
<td>β1</td>
<td>– –</td>
<td>renal</td>
<td>6–7</td>
<td>1</td>
</tr>
<tr>
<td>bisoprolol</td>
<td>β1</td>
<td>– –</td>
<td>hepatic and renal</td>
<td>10–12</td>
<td>1</td>
</tr>
<tr>
<td>carvedilol</td>
<td>α1, β1, β2</td>
<td>– ++</td>
<td>hepatic</td>
<td>6–10</td>
<td>1</td>
</tr>
<tr>
<td>labetalol</td>
<td>α1, β1, β2</td>
<td>– +</td>
<td>hepatic</td>
<td>6–8</td>
<td>2</td>
</tr>
<tr>
<td>metoprolol</td>
<td>β1</td>
<td>– +</td>
<td>hepatic</td>
<td>3–5 (conventional tablet)</td>
<td>1–2 (conventional tablet)</td>
</tr>
<tr>
<td>oxprenolol</td>
<td>β1, β2</td>
<td>+ +</td>
<td>hepatic</td>
<td>1–3</td>
<td>2–3</td>
</tr>
<tr>
<td>pindolol</td>
<td>β1, β2</td>
<td>++ +</td>
<td>hepatic and renal</td>
<td>3–4</td>
<td>2–3</td>
</tr>
<tr>
<td>propranolol</td>
<td>β1, β2</td>
<td>– ++</td>
<td>hepatic</td>
<td>3–6</td>
<td>2–3</td>
</tr>
</tbody>
</table>

ISA—intrinsic sympathomimetic activity

**Table 02-07 Drugs which may prolong QT interval**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>antiarrhythmics</td>
<td>amiodarone, disopyramide, procainamide, quinidine, sotalol</td>
</tr>
<tr>
<td>antidepressants</td>
<td>TCAs</td>
</tr>
<tr>
<td>antipsychotics</td>
<td>amisulpride, droperidol, haloperidol, pimozide, quetiapine, thioridazine</td>
</tr>
<tr>
<td>anti-infectives</td>
<td>artemether with lumefantrine, chloroquine, clarithromycin, erythromycin, fluconazole, gatifloxacin, mefloquine, moxifloxacin, pentamidine, quinine, voriconazole</td>
</tr>
<tr>
<td>miscellaneous</td>
<td>arsenic trioxide, cisapride, dolasetron, methadone, tacrolimus, vardenafil</td>
</tr>
</tbody>
</table>

*in therapeutic doses
<table>
<thead>
<tr>
<th>Indication and drug</th>
<th>Comments and alternative drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention of cardiovascular disease</strong></td>
<td></td>
</tr>
<tr>
<td>aspirin</td>
<td>low risk (isolated hypertension or diabetes): benefit of aspirin in preventing MI may be offset by risk of GI adverse effects in women: aspirin lowers risk of stroke but no evidence of benefit in terms of MI or death from cardiovascular causes in women &lt;65 years</td>
</tr>
<tr>
<td>Stable angina</td>
<td>use clopidogrel if allergic to aspirin</td>
</tr>
<tr>
<td>aspirin</td>
<td>Unstable angina (see also Acute coronary syndromes without ST-segment elevation)</td>
</tr>
<tr>
<td>aspirin with heparin (or LMWH) for 2–8 days then aspirin alone</td>
<td>combining aspirin with clopidogrel for at least 1 month and up to 12 months, inue aspirin or in acute phase, consider combining aspirin with low dose nd glycoprotein IIb/IIIa inhibitor</td>
</tr>
<tr>
<td>Acute MI</td>
<td>use clopidogrel if allergic to aspirin</td>
</tr>
<tr>
<td>aspirin with thrombolytic agent</td>
<td>warfarin may be preferred to aspirin if complications exist (AF, thromboembolism, intraventricular thrombosis, ventricular aneurysm)</td>
</tr>
<tr>
<td>Post MI</td>
<td>combination of warfarin and aspirin is effective but increases risk of bleeding</td>
</tr>
<tr>
<td>Venous aortocoronary bypass grafting</td>
<td>aspirin</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td></td>
</tr>
<tr>
<td>aspirin with low dose heparin and glycoprotein IIb/IIIa inhibitor</td>
<td></td>
</tr>
<tr>
<td>Post-intracoronary stenting</td>
<td>use aspirin with clopidogrel if allergic to aspirin</td>
</tr>
<tr>
<td>aspirin with clopidogrel for at least 1 month and up to 12 months, then aspirin alone</td>
<td>clopidogrel is not approved for this indication, but was effective in clinical trials and is safer than ticlopidine</td>
</tr>
<tr>
<td>Valve prosthesis</td>
<td>use aspirin with warfarin in patients with mechanical valve prosthesis and embolic risk factors</td>
</tr>
<tr>
<td>warfarin</td>
<td></td>
</tr>
<tr>
<td>Acute treatment of ischaemic stroke</td>
<td>aspirin</td>
</tr>
<tr>
<td>Primary prevention of stroke in AF</td>
<td>high risk (mitral stenosis, valve prosthesis): use warfarin other patients: choice between aspirin and warfarin depends on risk of bleeding with warfarin versus risk of embolism, see Atrial fibrillation, Prevent thromboembolic complications</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention of stroke</td>
<td>use clopidogrel if allergic to aspirin</td>
</tr>
<tr>
<td>aspirin or aspirin with dipyridamole</td>
<td>in AF use warfarin instead</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>use clopidogrel if allergic to aspirin</td>
</tr>
<tr>
<td>aspirin</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 03 RESPIRATORY SYSTEM

03.01 BRONCHODILATORS

03.01 01 Beta 2 agonists

EPINEPHRIN (ADRENALINE)

Mode of action
Epinephrine is an endogenous catecholamine which is the active principle of the adrenal medulla. It acts directly on both Alpha and Beta adrenergic receptors of tissues innervated by sympathetic nerves except the sweat glands and the arteries of the face. Epinephrine relaxes bronchial smooth muscle by stimulation of beta receptors and constricts bronchial arterioles by stimulation of Alpha receptors. In patients with bronchial constriction the drug relieves bronchospasm, reduces congestion and edema, and increases tidal volume and vital capacity.

Indications
Severe allergic reactions including anaphylactic shock, life-threatening angioedema, Bronchospasm and croup.

Contraindications
There are no absolute contraindications to adrenaline in severe life-threatening allergic reactions; adrenaline is often life-saving.

Specific considerations
Ischaemic heart and/or cerebrovascular disease: increased sensitivity to sympathomimetic effects.

Adverse effects
Central nervous system: Fear, anxiety, tenseness, restlessness, headache, tremor, dizziness, lightheadedness, nervousness, sleeplessness, excitability, and weakness.
Gastro intestinal: Nausea, vomiting.
Cardiovascular: Adrenaline causes Electrocardiographic changes including a decrease in the T-wave amplitude in all leads in normal persons. Disturbances of cardiac rhythm and rate may result in palpitation and tachycardia. In patients with coronary insufficiency or ischemic heart disease Adrenaline may aggravate or precipitate angina pectoris by increasing cardiac work and accentuating the insufficiency of the coronary circulation. Adrenaline may cause potentially fatal ventricular arrhythmias including fibrillation especially in patients with organic heart disease. Repeated injections of Adrenaline can cause necrosis due to vascular constriction at the injection site.

Dosage
Anaphylaxis, bronchospasm
Adult, child
IM 10 micrograms/kg (0.01 mL/kg adrenaline 1:1 000) up to 500 micrograms (0.5 mL).
IV 5 micrograms/kg (0.05 mL/kg adrenaline 1:10 000) as 0.5–1 mL aliquots every 1–2 minutes into the side-arm of a fast flowing IV infusion.
Repeat IM or IV dose every 5 minutes as required.
IV infusion 0.25 micrograms/kg/minute initially then titrate according to BP.

Croup
0.5 mg/kg nebulised (0.5 mL/kg adrenaline 1:1 000); maximum 5 mg (5 mL).

Adrenaline for self-administration
Adult, child >30 kg, 0.3 mg IM (EpiPen®).
Child 15–30 kg, 0.15 mg IM (EpiPen Jr®).

Administration instructions
Use a 0.5 mL or 1 mL syringe to measure small volumes of adrenaline.
If 1:10 000 is required and 1:1 000 is the only strength available, dilute 1 mL of 1:1 000 with 9 mL of sodium chloride 0.9% to make a 1:10 000 solution.
IM route is regarded as safer than IV; SC administration is not recommended in anaphylaxis as absorption is erratic. Inject IM adrenaline into anterolateral aspect of thigh; do not inject into hands, feet, ears, nose, genitals or buttocks.
IV administration is necessary when hypovolaemic shock occurs or response to IM is inadequate; use dilute form (1:10 000), give slowly and monitor ECG. IV infusion is used when duration of response to IV slow bolus is short.

Patient counselling
Make sure anyone who may need to give you adrenaline is taught how to recognize when you need it and how to give it.
Seek medical advice as soon as possible after you have used adrenaline because further doses may be required and should be given by a doctor.

Keeping adrenaline handy may be difficult; it must be kept in the dark and below 25°C, but not refrigerated; a portable cooler is needed on hot days.

Note the use by date for your adrenaline and arrange a new supply in advance.

**Practice points**

- Ampoules contain 1 mg adrenaline, i.e.:
  - adrenaline 1:1 000 = 1 mg in 1 mL
  - adrenaline 1:10 000 = 1 mg in 10 mL

- Use a 0.5 mL or 1 mL syringe to measure small volumes of adrenaline

- If 1:10 000 is required and 1:1 000 is the only strength available, dilute 1 mL of 1:1 000 with 9 mL of 0.9% sodium chloride to make a 1:10 000 solution

- SC administration is not recommended in anaphylaxis as absorption is erratic; IV infusion is used when duration of response to IM or IV slow bolus is short

- When giving IV adrenaline use 1:10 000 (dilute form), give slowly and use ECG monitoring

- Glucagon may be useful for adrenaline resistant anaphylaxis in patients on beta-blockers

- Inject IM adrenaline into anterolateral aspect of thigh; do not inject into hands, feet, ears, nose, genitals or buttocks

- Adrenaline inhalers are available via SAS but should not be used to treat severe allergic reactions because patients are unable to comply with the number of puffs needed to achieve an adequate dose

- Do not withhold adrenaline in severe life-threatening allergic reactions because of concerns about the risk of drug interactions.

**Products**

**EPINEPHRINE AMPS 1 MG/AMP 1 ML AMP (ADRENALINE®)**

**FORMOTEROL**

Also known as eformoterol

**Mode of action**

Relax bronchial smooth muscle by stimulating beta2 adrenoceptors (Long acting B2 agonist).

**Indications**

Maintenance treatment of asthma (in particular, nocturnal and exercise-induced asthma) in patients receiving inhaled or oral corticosteroids, Maintenance treatment of COPD, Symptom relief of asthma in patients already receiving inhaled corticosteroids and twice daily dosing of formoterol (Oxis Turbuhaler®)

**Combination with budesonide.**

Maintenance treatment of asthma inadequately controlled with inhaled corticosteroids or when stabilized on formoterol and budesonide.

**Short acting beta2 agonists**

Acute asthma, Symptom relief during maintenance treatment of asthma and COPD.

**Protection against exercise-induced asthma, Long acting beta2 agonists.**

Maintenance treatment of asthma (including nocturnal and exercise-induced asthma) in patients receiving inhaled or oral corticosteroids, Maintenance treatment of COPD.

**Contraindications**

Allergy to either main ingredient or to preservatives in multi-dose solutions for nebulisation.

**Specific considerations**

Pregnancy: Limited experience but asthma control is paramount; ADEC category B3.
Breastfeeding: No data available; should be safe to use.

For oral and parenteral use of Beta2 agonists consider:
Cardiovascular disorders (including hypertension, heart failure, ischaemic heart disease, arrhythmias): risk of cardiovascular adverse effects.
Hyperthyroidism: risk of cardiovascular adverse effects.
Diabetes: risk of hyperglycaemia.

Treatment with other sympathomimetic amines: may increase adverse effects (e.g. tremor, tachycardia); avoid combination or adjust dose as necessary.

Elderly: Start with a lower dose than the usual adult dosage; gradually increase if necessary.

**Adverse effects**

Incidence and severity of adverse effects depend on dosage and route of administration.
Common: tremor, palpitations, headache.
Infrequent: hyperglycaemia (high dose), tachycardia, muscle cramps, agitation, hyperactivity in children, insomnia.
Rare: paradoxical bronchospasm, allergic reactions including urticaria and angioedema.

**Dosage**

**Adult**
DPI (Foradil®), 12–24 micrograms (1–2 capsules) inhaled twice daily.
DPI (Oxis Turbuhaler®), 6–12 micrograms inhaled twice daily, maximum daily dose 48 micrograms; additional doses may be given for short term symptom relief up to a maximum daily dose of 72 micrograms; reassess treatment if required on >3 consecutive days.
Child >5 years: DPI (Foradil®), 12 micrograms (1 capsule) inhaled twice daily.
Child >12 years: DPI (Oxis Turbuhaler®), 6–12 micrograms inhaled twice daily, maximum daily dose 24 micrograms.

**Combination with budesonide**
Adult: DPI, 1–2 inhalations twice daily (of either strength product).
Child >12 years: DPI, 1–2 inhalations twice daily (of 6 micrograms formoterol with 200 micrograms budesonide).

**Patient counseling**
Use this medicine every day even if you feel better
Tell your doctor as soon as possible if you need to use this medicine in higher doses or more frequently than prescribed.

**Practice points**
- in asthma, formoterol is not a substitute for inhaled corticosteroid treatment and they must be used together
- should not be used for symptom relief in asthma except in patients already receiving inhaled corticosteroids and formoterol
- duration of protection against exercise-induced asthma may decline with regular use
- inhaled short acting beta₂ agonists are first line bronchodilators in acute asthma
- consider preventive anti-inflammatory treatment if short acting beta₂ agonists are needed 3 or more times a week
- routes of administration:
  - inhaled preparations preferred because of fewer systemic adverse effects and faster onset of action
  - for very young children, use a small volume spacer with face mask rather than an oral preparation
  - parenteral preparations may be used in acute severe asthma; they are associated with more adverse effects
  - a nebuliser is not recommended for maintenance treatment or treatment of acute asthma in adults or children but may be used for treatment of severe or life-threatening acute asthma
  - teach, check and review inhaler technique regularly, especially when asthma control is poor
  - oral administration of salbutamol or terbutaline is rarely used

**Products**
- FORMOTEROL CAPS 12 MCG/CAP (AS FUMERATE) 30 DOSE (FORADIL®)
- FORMOTEROL TURBUHALER 4.5 MCG (AS FUMERATE) 60 DOSE (OXIS®)
- FORMOTEROL TURBUHALER 9 MCG (AS FUMERATE) 60 DOSE (OXIS®)

**SALBUTAMOL**
Also known as albuterol.

**Mode of action**
Relax bronchial smooth muscle by stimulating beta₂ adrenoceptors (Short acting B₂ agonist).

**Indications**
**Acute asthma**
Symptom relief during maintenance treatment of asthma and COPD.
Protection against exercise-induced asthma.
Management of preterm labour.

**Combination with ipratropium**
Maintenance treatment in COPD insufficiently controlled by a single bronchodilator
Short acting beta₂ agonist

**Contraindications**
Allergy to soya lecithin or related food products such as soya bean and peanuts
Allergy to main ingredient or to preservatives in multi-dose solutions for nebulisation.

**Specific considerations**
For oral and parenteral use consider:
Cardiovascular disorders (including hypertension, ischaemic heart disease, heart failure, arrhythmias): risk of cardiovascular adverse effects.
Hyperthyroidism: risk of cardiovascular adverse effects.
Diabetes: risk of hyperglycaemia.
Treatment with other sympathomimetic amines: may increase adverse effects (tremor, tachycardia, headache); avoid combination or adjust dose as necessary.
Elderly: Start with a lower dose than the usual adult dosage; gradually increase if necessary.
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Safe to use.

**Adverse effects**
Incidence and severity of adverse effects depend on dosage and route of administration.
Common: tremor, palpitations, headache
Infrequent: hyperglycaemia (high dose), tachycardia, muscle cramps, agitation, hyperactivity in children, insomnia
Rare: paradoxical bronchospasm, allergic reactions including urticaria and angioedema
Serious hypokalaemia may occur with high doses of beta2 agonists; may be worsened by theophyllines, corticosteroids, diuretics and hypoxia.

**Dosage**

**Adult**
MDI, 100–200 micrograms (1–2 inhalations) as required, or 5–15 minutes before exercise. Repeat 3–4 times daily as necessary.
DPI (Diskhaler, Rotacaps), 200–400 micrograms (1–2 inhalations) as required, or 5–15 minutes before exercise. Repeat 3–4 times daily as necessary.
Neb, 2.5–5 mg, repeat 3–4 times daily as necessary.
Oral, 2–4 mg 3–4 times daily.
IV injection, 200–300 micrograms over 1 minute, repeat after 15 minutes as required.
IV infusion, loading dose, 200 micrograms over 1 minute. Initial infusion, 5 micrograms/minute; adjust according to response, usually increase to 10–20 micrograms/minute.
SC/IM, 500 micrograms, repeat every 4 hours as necessary.

**Child**
MDI, 100–200 micrograms (1–2 inhalations) as required, or 5–15 minutes before exercise. Repeat 3–4 times daily as necessary.
DPI (Diskhaler, Rotacaps), 200–400 micrograms (1–2 inhalations) as required, or 5–15 minutes before exercise. Repeat 3–4 times daily as necessary.
neb,<2 years, 0.1 mg/kg up to 2.5 mg, repeat 3–4 times daily as necessary.
neb,>2 years, 2.5–5 mg, repeat 3–4 times daily as necessary.
oral,<6 years, 100–150 micrograms/kg 3–4 times daily.
oral,>6 years, 80 micrograms/kg 3–4 times daily.
IV injection, 50–200 micrograms over 1 minute, repeat after 15 minutes as required.
IV infusion, loading dose 5–7.5 micrograms/kg over 1 minute. Infusion, 5–7.5 micrograms/kg/hour.
SC/IM, 10–20 micrograms/kg, repeat every 4 hours as necessary.

**Combination with ipratropium**
Consider use for patients stabilised on similar doses of each drug.

**Administration instructions**
Multi-dose solution for nebulisation may need dilution with sodium chloride 0.9% to obtain a final volume suitable for the nebuliser used.

**Patient counseling**
Regularly clean mouthpiece of your inhaler to prevent blockage of the nozzle.
Tell your doctor as soon as possible if you need to use this medicine in higher doses or more frequently than prescribed.

**Practice points**
- reserve nebuliser solution for life-threatening acute asthma; oral administration rarely used
- parenteral route may be used in acute severe asthma, but has a higher risk of adverse effects
inhaled short acting beta_2 agonists are first line bronchodilators in acute asthma
consider preventive anti-inflammatory treatment if short acting beta_2 agonists are needed 3 or more times a week
routes of administration:
  - inhaled preparations preferred because of fewer systemic adverse effects and faster onset of action
  - for very young children, use a small volume spacer with face mask rather than an oral preparation
  - parenteral preparations may be used in acute severe asthma; they are associated with more adverse effects
  - a nebuliser is not recommended for maintenance treatment or treatment of acute asthma in adults or children but may be used for treatment of severe or life-threatening acute asthma
  - teach, check and review inhaler technique regularly, especially when asthma control is poor
  - oral administration of salbutamol or terbutaline is rarely used

Products
SALBUTAMOL INHAULER 100 MCG/PUFF (AS SULFATE) 200 DOSE (AEROLIN®, ASTHALIN®, SALBUTIS®, VENTOLIN®, VENTAL®)
SALBUTAMOL SOLUTION 5 MG/ML (AS SULFATE) 20 ML BOTTLE (VENTOLIN®)
SALBUTAMOL SYRUP 2 MG/5 ML (AS SULFATE) 120 ML BOTTLE (ASMADIL®, BUTALIN®, VENTOL®)
SALBUTAMOL TABS 2 MG (AS SULFATE) (ASMADIL®, ASMANORE®, BUTALIN®, MEDOLIN®)

SALMETEROL
Mode of action
Relax bronchial smooth muscle by stimulating beta_2 adrenoceptors (Long acting B_2 agonist).
Indications
Maintenance treatment of asthma (including, nocturnal and exercise-induced asthma) in patients receiving inhaled or oral corticosteroids, Maintenance treatment of COPD.
Combination with fluticasone
Maintenance treatment of asthma in patients inadequately controlled with inhaled corticosteroids or in patients previously stabilized on salmeterol and fluticasone
Severe COPD with repeated exacerbations inadequately controlled with regular beta_2 agonist therapy.
Contraindications
Allergy to main ingredient or to preservatives in multi-dose solutions for nebulisation
Specific considerations
For oral and parenteral use consider:
Cardiovascular disorders (including hypertension, ischaemic heart disease, heart failure, arrhythmias): risk of cardiovascular adverse effects.
Hyperthyroidism: risk of cardiovascular adverse effects.
Diabetes: risk of hyperglycaemia.
Treatment with other sympathomimetic amines: may increase adverse effects (tremor, tachycardia, headache); avoid combination or adjust dose as necessary.
Elderly: Start with a lower dose than the usual adult dosage; gradually increase if necessary.
Pregnancy: Limited experience but asthma control is paramount; ADEC category B3.
Breastfeeding: Safe to use.
Adverse effects
Incidence and severity of adverse effects depend on dosage and route of administration.
Common: tremor, palpitations, headache.
Infrequent: hyperglycaemia (high dose), tachycardia, muscle cramps, agitation, hyperactivity in children, insomnia.
Rare: paradoxical bronchospasm, allergic reactions including urticaria and angioedema.
Dosage
Adult, child >4 years:
MDI/DPI, 50 micrograms twice daily (up to 100 micrograms twice daily in more severe airways obstruction in adults).
**Combination with fluticasone**

For additional information see FLUTICASONE (inhaled).

Consider use for patients stabilised on similar doses of each drug.

**Adult, asthma**
MDI, 2 inhalations twice daily (of 25 micrograms salmeterol with 50, 125 or 250 micrograms fluticasone).
DPI, 1 inhalation twice daily (of 50 micrograms salmeterol with 100, 250 or 500 micrograms fluticasone).

**Adult, COPD**
MDI, 2 inhalations twice daily (of 25 micrograms salmeterol with 125 or 250 micrograms fluticasone).
DPI, 1 inhalation twice daily (of 50 micrograms salmeterol with 250 or 500 micrograms fluticasone).

**Child >4 years, asthma**
MDI, 2 inhalations twice daily (of 25 micrograms salmeterol with 50 micrograms fluticasone).
DPI, 1 inhalation twice daily (of 50 micrograms salmeterol with 100 micrograms fluticasone).

**Patient counseling**
Do not use this drug to relieve symptoms of an asthma attack; use short acting reliever instead.
Use this medicine every day even if you are feeling better.
Tell your doctor as soon as possible if you need to use this medicine in higher doses or more frequently than prescribed.

**Practice points**
- in asthma, salmeterol is not a substitute for inhaled corticosteroid treatment and these must be used together
- should not be used for acute symptom relief or in the management of acute asthma
- duration of protection against exercise-induced asthma may decline with regular use
- consider using the lower recommended dose of salmeterol with fluticasone in those patients with COPD who are at greater risk of corticosteroid adverse effects
- inhaled short acting beta₂ agonists are first line bronchodilators in acute asthma
- consider preventive anti-inflammatory treatment if short acting beta₂ agonists are needed 3 or more times a week
- routes of administration:
  - inhaled preparations preferred because of fewer systemic adverse effects and faster onset of action
  - for very young children, use a small volume spacer with face mask rather than an oral preparation
  - parenteral preparations may be used in acute severe asthma; they are associated with more adverse effects
- a nebuliser is not recommended for maintenance treatment or treatment of acute asthma in adults or children but may be used for treatment of severe or life-threatening acute asthma
- teach, check and review inhaler technique regularly, especially when asthma control is poor
- oral administration of salbutamol or terbutaline is rarely used

**Products**
SALMETEROL DISCUS 50 MCG/PUFF 60 DOSE (SEREVENT®)
SALMETEROL INHALER 25 MCG 120 DOSE PER BOTTLE (SEREVENT®)
SALMETEROL+FLUTICASONE DISKUS 50+250 MCG/DOSE 60 DOSE (SERETIDE®)
SALMETEROL+FLUTICASONE DISKUS 50+100 MCG/DOSE 60 DOSE (SERETIDE®)

**03.01.02 Anticholinergic bronchodilators**

**IPRATROPIUM**

**Mode of action**
Promote bronchodilation by inhibiting cholinergic bronchomotor tone.

**Indications**
Severe acute asthma.
Maintenance treatment in COPD and severe asthma.

**Combination with salbutamol**
Maintenance treatment in COPD in patients insufficiently controlled by a single bronchodilator.

**Contraindications**
Allergy to soya lecithin or related food products such as soya bean and peanuts (MDI only).

**Specific considerations for using Anticholinergic bronchodilators.**
Glaucoma, prostatic hypertrophy: risk of aggravation.
Pregnancy: Limited experience; ADEC category B1.
Breastfeeding: Safe to use.

**Adverse effects**
Common: dry mouth, throat irritation.
Rare: urinary retention, constipation, acute angle closure glaucoma, allergy (angioedema, anaphylaxis, rash).

**Dosage**

**Adult**
COPD and severe asthma
MDI, 40 micrograms, repeat 3–4 times daily as necessary; up to 80 micrograms 3–4 times daily may be needed.
Neb, 250–500 micrograms up to 3–4 times daily.
Severe acute asthma
Neb, 500 micrograms every 2 hours with salbutamol.
Child, severe acute asthma
MDI, 40–80 micrograms every 20 minutes, up to 3 doses in the first hour.
Neb, 250 micrograms every 20 minutes, up to 3 doses in the first hour.

**Administration instructions**
Dilute solution for nebulisation to 2–3 mL with sodium chloride 0.9%.

**Patient counseling**
Do not use for immediate relief of symptoms.
Do not reduce or stop your inhaled corticosteroids even if you feel better after starting this drug.
Do not let the mist from the nebuliser get into your eyes. Close your eyes or wear eye protection.
Tell your doctor if you have any eye pain or discomfort, blurred vision or visual halos.

**Practice points**
- use as alternative to, or combined with, beta2 agonists in COPD
- consider ipratropium with salbutamol product for patients with COPD stabilized on similar doses of single ingredient.

**Products**
- **IPRATROPIUM INHALER 20 MCG/PUFF (AS BROMIDE) 200 DOSE PER BOTTLE (ATROVENT®, IPRATROPIUM BROMIDE®)**
- **IPRATROPIUM SOLUTION 500 MCG/VIAL (AS BROMIDE) 2 ML VIAL (ATROVENT®)**

**TIOTROPIUM**

**Mode of action**
Promote bronchodilation by inhibiting cholinergic bronchomotor tone.

**Indications**
Maintenance treatment in COPD.

**Specific considerations**
Glaucoma, prostatic hypertrophy: risk of aggravation.
Pregnancy: Limited experience; ADEC category B1.
Breastfeeding: Safe to use.

**Adverse effects**
Common: dry mouth, throat irritation.
Rare: urinary retention, constipation, acute angle closure glaucoma, palpitations, allergy (angioedema, anaphylaxis, rash).

**Dosage**
DPI, 18 micrograms (1 capsule) inhaled once daily.

**Patient counseling**
Do not use for immediate relief of symptoms.
Do not allow the powder to come in contact with your eyes.
Tell your doctor if you have any eye pain or discomfort, blurred vision or visual halos.

**Products**
- **TIOTROPIUM INHALER POWDER HARD CAPS 18 MCG/CASP (AS BROMIDE) + HANDIHALER (SPIRIVA®)**

03.01.03 Compound Bronchodilator Preparations
FORMOTEROL+BUDESONIDE
For information about BUDESONIDE (inhaled), see Corticosteroids (inhaled).

Products
FORMOTEROL+BUDESANIDE TURBUHALER 4.5+160 MCG/PUFF 60 DOSE (SYMBICORT®)

IPRATROPİUM + SALBUTAMOL

Products
IPRATROPİUM INHALER+SALBUTAMOL 20+100 MCG/PUFF 200 DOSE PER CAN (COMBIVENT®)

IPRATROPİUM VIAL + SALBUTAMOL 500 MCG+2.5 MG/VIAL 2.5 ML VIAL (COMBIVENT®)

03.01.04 Theophylline derivatives

AMINOPHYLLİNE

Mode of action
Not entirely understood. Possible effects include anti-inflammatory effects, bronchial smooth muscle relaxation, increase in diaphragm contractility and CNS stimulation.

Indications
Severe airways obstruction, including acute asthma, maintenance treatment in severe asthma and COPD.

Specific considerations
Gastro-oesophageal reflux disease: theophylline increases gastric acid secretion and relaxes gastro-oesophageal sphincter.
Arrhythmia: may be exacerbated.
Heart failure, pulmonary oedema, severe hypoxia: reduces theophylline clearance; smaller dose may be needed.
Thyroid dysfunction: hyperthyroidism increases theophylline clearance while hypothyroidism decreases its clearance; monitor theophylline concentration and adjust dose as needed when treating thyroid dysfunction.
Smoking: increases theophylline clearance; larger dose may be needed.
Epilepsy: theophyllines may lower seizure threshold.
Acute febrile illness, viral infections: possibly increases theophylline concentration.
Treatment with beta2 agonists: increases risk of hypokalaemia; monitor potassium concentration in severe asthma.
Hepatic impairment: require a lower dose.
Elderly: Theophylline clearance decreases with age; use a lower dose.
Pregnancy: monitor theophylline concentration as pharmacokinetics (and dose requirement) may alter; ADEC category A.
Breastfeeding: irritability has been reported in infants; keep theophylline concentration as low as possible; use inhaled bronchodilators in preference.

Adverse effects
Theophylline has a narrow therapeutic index; toxicity is closely related to high concentrations.
Common: usea, vomiting, diarrhoea, gastro-oesophageal reflux, headache, insomnia, irritability, anxiety, tremor, palpitations.
Rare: Sizures, cardiac arrhythmias (high concentrations), tachycardia Alergic dermatitis (due to ethylenediamine component of aminophylline), sudden death.

Dosage
Adult not previously treated with theophylline injection, loading dose 5 mg/kg (give over 20 minutes). IV infusion, maintenance 0.5 mg/kg/hour.
Child not previously treated with theophylline: injection, loading dose 5–10 mg/kg (give over 20 minutes). IV infusion, maintenance 1 mg/kg/hour.

Dose equivalence
Aminophylline is the ethylenediamine salt of theophylline; 1 mg aminophylline is equivalent to 0.8 mg theophylline.

Concentration monitoring
Therapeutic range: plasma theophylline concentrations 10–20 mg/L (55–110 micromol/L).

Administration instructions
Do not use aminophylline injection if crystals are present. Do not mix aminophylline with other drugs. Slow IV administration required (<20–25 mg/minute) to reduce risk of hypotension, seizures and arrhythmias.
**Patient Counselling**
This medicine interacts with many other drugs; ask your doctor or pharmacist before using any other medicines including herbal and over-the-counter products.

**Practice points**
- do not give to patients previously treated with theophylline unless plasma concentration is available to guide dosage
- plasma monitoring is highly recommended
- may be used in acute severe asthma; reserve use for those unresponsive to combined treatment with inhaled short acting beta₂ agonists, inhaled ipratropium and systemic corticosteroids
- not recommended for routine use in COPD exacerbations; consider use if response to nebulised bronchodilators is inadequate
- theophylline derivatives have a narrow therapeutic index; adjust dosage individually according to clinical response and plasma concentrations
- many people experience minor adverse effects with plasma concentrations below or within the therapeutic range; minimise adverse effects by using a low initial dose and by increasing the dose at intervals of no less than 3 days
- use of theophylline derivatives is declining due to narrow therapeutic index and availability of alternative drugs, eg long acting beta₂ agonists; they may still be useful in patients with moderate or severe asthma as an alternative to increasing inhaled corticosteroid dosage.

**Products**
**AMINOPHYLINE AMPS 250 MG/AMP (AS HYDRATE) 10 ML AMP (AMINOPHYLLINE®)**

**THEOPHYLLINE**

**Mode of action**
Not entirely understood. Possible effects include anti-inflammatory effects, bronchial smooth muscle relaxation, increase in diaphragm contractility and CNS stimulation.

**Indications**
Maintenance treatment in severe asthma and COPD.

**Specific considerations**
Same as aminophylline

**Adverse effects**
Theophylline has a narrow therapeutic index; toxicity is closely related to high concentrations.
Common: nausea, vomiting, diarrhoea, gastro-oesophageal reflux, headache, insomnia, irritability, anxiety, tremor, palpitations.
Rare: seizures, cardiac arrhythmias (high concentrations), tachycardia.

**Dosage**
Maximum: 900 mg daily for maintenance dosage.
Adult, child >6 months with no risk factors for decreased theophylline clearance
Initial dose, 10 mg/kg daily; maximum 300 mg daily. If initial dose is tolerated, increase dose after 3 days.
First increment, 13 mg/kg daily; maximum 450 mg daily. If the first increase is tolerated, increase dose after 3 days.
Second increment, 16 mg/kg daily; maximum 600 mg daily. Measure plasma concentration after 3 days at the highest tolerated dose.
Controlled release preparations are given every 12 hours; conventional preparations are given every 6 hours.

**Concentration monitoring**
Therapeutic range: trough (predose) theophylline plasma concentrations 10–20 mg/L (55–110 micromol/L); plasma concentrations at the lower end of the range, eg 9–10 mg/L (50–55 micromol/L), also seem to be effective.
Monitor plasma concentration at initiation of treatment, if drug regimen is altered, if there is prolonged fever, if adverse effects suspected and if patient stops or starts smoking.

**Patient Counselling**
This medicine may be taken with food to reduce stomach upset.
Do not crush or chew Nuelin SR® tablets.
This medicine interacts with many other drugs; ask your doctor or pharmacist before using any other medicines including herbal and over-the-counter products.

**Practice points:**
- oral liquid contains 50% sugar
controlled release theophylline may be used as adjunctive treatment in severe persistent asthma; it may also be useful for nocturnal asthma although long acting beta₂ agonists are effective and safer alternatives

- use in COPD is limited to patients who remain symptomatic despite optimal use of inhaled therapy
- theophylline derivatives have a narrow therapeutic index; adjust dosage individually according to clinical response and plasma concentrations
- many people experience minor adverse effects with plasma concentrations below or within the therapeutic range; minimise adverse effects by using a low initial dose and by increasing the dose at intervals of no less than 3 days
- use of theophylline derivatives is declining due to narrow therapeutic index and availability of alternative drugs, eg long acting beta₂ agonists

**Products**

THEOPHYLLINE CAPS/TABS 200 MG (ANHYDROUS) (THEOLIN®, UNIPHYLLINE®)
THEOPHYLLINE TABS 300 MG (ANHYDROUS) (QUIBRON®, THEOLIN®, UNIPHYLLINE®)

### 03.02 CORTICOSTEROIDS (INHALED)

**BECLOMETHASONE (INHALED)**

**Mode of action**
Reduce bronchial mucosal inflammation and bronchial hyper-reactivity.

**Indications.**
Marketed: Maintenance treatment in persistent asthma, Severe COPD (fluticasone with salmeterol).
Accepted: Maintenance treatment in severe COPD with frequent exacerbations.

**Specific considerations**
- Pregnancy: Safe to use; ADEC category B3.
- Breastfeeding: Safe to use.

**Adverse effects**
- Common: dysphonia, oropharyngeal candidiasis, facial skin irritation following nebulisation.
- Rare: allergic reactions, including bronchospasm, rash, urticaria and angioedema.

**Systemic adverse effects**
Occurrence of systemic adverse effects depends on amount of systemic absorption, which is influenced by dosage, duration of treatment and the delivery system used.

**REDUCE SYSTEMIC ABSORPTION**
Inhale corticosteroids using MDI with a spacer, then rinse mouth with water, gargle and spit out.
Adrenal impairment: increased risk with higher doses particularly in older patients.
Bone density loss: clinical implications concerning risk of osteoporosis and fracture are still unknown.
Glaucoma, cataract: risk may be increased.
Skin thinning and bruising: may occur with high doses.
Impaired growth: inhaled corticosteroids may reduce growth velocity, mainly in the first year of treatment; effect on growth of other organs (eg brain and lung) is not well defined; poorly controlled asthma may also cause growth retardation.

**Dosage**
- Adult: MDI, 50–200 micrograms twice daily; up to 500 micrograms daily in severe persistent asthma. Consider specialist referral for patients who require >500 micrograms daily.
- Child >5 years: MDI, 50 micrograms twice daily; up to 400 micrograms daily in severe persistent asthma.

**Patient counseling**
- Do not use this drug for acute symptom relief; use short acting reliever.
- Do not reduce dosage or stop this drug unless advised by your doctor.
- Use a spacer with MDI; rinse mouth and throat after inhaling.
- Regularly clean mouthpiece of your inhaler to prevent blockage of the nozzle.
- Use this medicine every day even if you are feeling better; do not reduce dosage or stop this medicine unless your doctor tells you to.

**Practice points**
- in asthma most of the therapeutic benefit is achieved with a total daily dose of 100–250 micrograms; doses >500 micrograms daily are used in severe asthma and require specialist supervision
- dosage required depends on product and delivery device
- start at a dose likely to be effective, then reduce to the minimum dose needed to maintain control of asthma
• step down every 3 months by reducing dose by 25% if control of asthma has been achieved
• check inhaler technique and compliance regularly
• pregnant women should be encouraged to continue use of inhaled corticosteroids
• inhaled corticosteroids may be useful in patients with severe COPD (FEV₁ 50% or less) with frequent exacerbations (2 or more a year).

**Products**

**BECLOMETHASON INHALER 50 MCG/PUFF (AS DIPROPIONATE) 200 DOSE PER BOTTLE**
(AEROBEC®, BECOTIDE®, CLNIL®, FILAIR®, BECLOMETHASONE DIPROPIONATE®, BELOTIS®)

**BECLOMETHASON INHALER 250 MCG/PUFF (AS DIPROPIONATE) 200 DOSE PER BOTTLE**
(AEROBEC FORTE®, BECLOFORTE®, CLNIL®, FILAIR FORTE®, BELOTIS®)

**BUDESONIDE (INHALED)**

**Mode of action**
Reduce bronchial mucosal inflammation and bronchial hyper-reactivity.

**Indications**
Maintenance treatment in persistent asthma.

**Combination with formoterol**
Marketed Maintenance treatment of asthma inadequately controlled with inhaled corticosteroids or when stabilised on budesonide and formoterol:
Accepted: Maintenance treatment in severe COPD with frequent exacerbations.

**Specific considerations**
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Should be safe to use.

**Adverse effects**
Common: dysphonia, oropharyngeal candidiasis, facial skin irritation following nebulisation.
Rare: allergic reactions, including bronchospasm, rash, urticaria and angioedema.

**Systemic adverse effects**
Same as Beclomethasone.

**Dosage**

**Adult**
DPI, 100–400 micrograms twice daily (once daily dosing possible up to 400 micrograms daily); up to 2000 micrograms daily in severe persistent asthma. Consider specialist referral for patients who require >800–1000 micrograms daily.
Neb, 0.5–1 mg twice daily.

**Child**
DPI, 100–200 micrograms twice daily; up to 800–1000 micrograms daily in severe persistent asthma.
Neb, 0.25–0.5 mg twice daily.

**Croup**
Neb, 2 mg as a single dose; repeat every 12 hours for 24–48 hours if clinically indicated.

**Combination with formoterol**
For additional information see FORMOTEROL
Adult: DPI, 1–2 inhalations twice daily (of either strength product).
Child >12 years: DPI, 1–2 inhalations twice daily (of 6 micrograms formoterol with 200 micrograms budesonide).

**Administration instructions**
Nebulisation of budesonide requires a high flow nebuliser (8 L/minute). Cover eyes during nebulisation and wash face afterwards. Consider using mouthpiece rather than mask.

**Patient counselling**
After using this medicine rinse your mouth with water, gargle and spit out.
Do not use this medicine for immediate relief of symptoms; use a short acting reliever.
Use this medicine every day even if you are feeling better; do not reduce dosage or stop this medicine unless your doctor tells you to.

**Practice points**
• in asthma most of the therapeutic benefit is achieved with a total daily dose of 200–500 micrograms; doses >800–1000 micrograms daily are used in severe asthma and require specialist supervision
• consider budesonide with formoterol product for patients with asthma on similar doses of single ingredient products
• dosage required depends on product and delivery device
• start at a dose likely to be effective, then reduce to the minimum dose needed to maintain control
• step down every 3 months by reducing dose by 25% if control has been achieved
• check inhaler technique and compliance regularly
• pregnant women should be encouraged to continue use of inhaled corticosteroids
• inhaled corticosteroids may be useful in patients with severe COPD (FEV1 50% or less) with frequent exacerbations (2 or more a year).

Products
BUDESONIDE POWDER 200 MCG/PUFF  100-200 DOSE PER BOTTLE (ESONIDE®)

FLUTICASONE (INHALED)
Mode of action
Reduce bronchial mucosal inflammation and bronchial hyper-reactivity.
Indications
Marketed Maintenance treatment in persistent asthma.
Acute asthma (nebulisations).
Combination with salmeterol
Maintenance treatment of asthma in patients inadequately controlled with inhaled corticosteroids or in patients stabilised on fluticasone and salmeterol.
Severe COPD with repeated exacerbations inadequately controlled with regular beta2 agonist therapy.
Accepted: Maintenance treatment in moderate-to-severe COPD.
Specific considerations
Pregnancy: Safe to use; ADEC category B3.
Breastfeeding: Should be safe to use.
Adverse effects
Common: dysphonia, oropharyngeal candidiasis, facial skin irritation following nebulisation
Rare: allergic reactions, including bronchospasm, rash, urticaria and angioedema
Systemic adverse effects
Same as Beclomethasone.
Dosage
Acute asthma: Adult, child 4-16 years, neb, 1 mg twice daily for 7 days.
Persistent asthma: Adult, MDI/DPI, 100-200 micrograms twice daily; up to 1000 micrograms daily in severe persistent asthma Consider specialist referral for patients who require >500 micrograms daily.
Adult with severe asthma requiring high dose inhaled corticosteroids or oral corticosteroids, neb, initially 2 mg twice daily then adjust according to response.
Child >1 year, MDI/DPI, 50–100 micrograms twice daily; up to 500 micrograms daily in severe persistent asthma Consider specialist referral for children <5 years who require >250 micrograms daily.
Combination with salmeterol
For additional information see SALMETEROL.
Adult, asthma
MDI, 2 inhalations twice daily (of 25 micrograms salmeterol with 50, 125 or 250 micrograms fluticasone).
DPI, 1 inhalation twice daily (of 50 micrograms salmeterol with 100, 250 or 500 micrograms fluticasone).
Adult, COPD
MDI, 2 inhalations twice daily (of 25 micrograms salmeterol with 125 or 250 micrograms fluticasone).
DPI, 1 inhalation twice daily (of 50 micrograms salmeterol with 250 or 500 micrograms fluticasone).
Child >4 years, asthma
MDI, 2 inhalations twice daily (of 25 micrograms salmeterol with 50 micrograms fluticasone).
DPI, 1 inhalation twice daily (of 50 micrograms salmeterol with 100 micrograms fluticasone).
Administration instructions
Solution for nebulisation may need dilution with sodium chloride 0.9% to obtain a final volume suitable for the nebuliser used. Cover eyes during nebulisation and wash face afterwards. Consider using mouthpiece rather than mask.
Patient counselling
Use a spacer with the metered dose inhaler.
After using this medicine rinse your mouth with water, gargle and spit out.
Do not use this medicine for immediate relief of symptoms; use a short acting reliever.
Use this medicine every day even if you are feeling better; do not reduce dosage or stop this medicine unless your
doctor tells you to.

Practice points
- in asthma most of the therapeutic benefit is achieved with a total daily dose of 100–250 micrograms; doses >500 micrograms daily are used in severe asthma and require specialist supervision
- further data are needed to clarify the place of nebulised fluticasone compared to systemic corticosteroids in acute asthma
- consider fluticasone with salmeterol combination products for patients with asthma stabilised on similar doses of single ingredient products
- dosage required depends on product and delivery device
- start at a dose likely to be effective, then reduce to the minimum dose needed to maintain control
- step down every 3 months by reducing dose by 25% if control has been achieved
- check inhaler technique and compliance regularly
- pregnant women should be encouraged to continue use of inhaled corticosteroids
- inhaled corticosteroids may be useful in patients with severe COPD (FEV₁ 50% or less) with frequent exacerbations (2 or more a year).

Products
FLUTICASONE INHALER 50 MCG/PUFF 120 DOSE (FLIXOTIDE®)
FLUTICASONE DISKUS INHALER 100 MCG/PUFF 60 DOSE (FLIXOTIDE®)

03.03 LEUKOTRINE-RECEPTOR ANTAGONISTS

MONTELUKAST
Mode of action
Inhibit the cysteinyl leukotriene receptor; antagonise airway smooth muscle contraction and inflammation caused by leukotrienes.
Indications
Maintenance treatment of asthma.
Specific considerations
Pregnancy: Limited experience; ADEC category B1.
Breastfeeding: Limited experience; should be safe to use.
Adverse effects
Common: headache, abdominal pain, diarrhea.
Rare: Churg–Strauss syndrome, allergic reaction including urticaria, angioedema and anaphylaxis.
Dosage
Adult. 10 mg once daily at bedtime.
Child 6–14 years, 5 mg once daily at bedtime.
Child 2–5 years, 4 mg once daily at bedtime.
Patient counselling
Do not use this drug to relieve symptoms of an asthma attack; use short acting reliever.
Children's tablets can be chewed.
Practice points
- do not substitute abruptly for inhaled or oral corticosteroids
- effect should be seen within days.
Products
MONTELUKAST TABS 4 MG (SINGULAIR®)

ZAFIRLUKAST
Mode of action
Inhibit the cysteinyl leukotriene receptor; antagonise airway smooth muscle contraction and inflammation caused by leukotrienes.
Indications
Maintenance treatment of asthma

Specific considerations
Hepatic impairment: Avoid use.
Children: No data in children <12 years.
Pregnancy: Limited experience; ADEC category B1.
Breastfeeding: Limited experience; should be safe to use.

Adverse effects
Common: headache, abdominal pain, diarrhea.
Rare: hepatitis, Churg–Strauss syndrome, allergic reaction including urticaria, angioedema and anaphylaxis.

Dosage
20 mg twice daily at least 1 hour before or 2 hours after meals; may be increased up to 40 mg twice daily.

Patient counseling
Do not use this drug to relieve symptoms of an asthma attack; use short acting reliever.
Tell your doctor immediately if you have nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine or jaundice.

Practice points
- stop treatment with zafirlukast and check liver enzymes if symptoms of hepatic dysfunction occur
- do not substitute abruptly for inhaled or oral corticosteroids
- effect should be seen within days.

Products
ZAFIRLUKAST TABS 20 MG (ACCOLATE®)

03.04 ANTIHISTAMINES

Antihistamines are divided into 2 groups: older, sedating drugs and newer, less sedating drugs, according to their potential for CNS depression. Individual response to specific antihistamines varies widely; it may be necessary to try a number of agents to see which is best tolerated and most effective.

Tachyphylaxis, necessitating an increase in dose, has been reported after several days of treatment with older antihistamines. However, nearly all of the recommended indications are for short term treatment. Antihistamines differ in their duration of action, incidence of drowsiness, and antimuscarinic effects; either a sedating or a non-sedating antihistamine may be used to treat an acute allergic reaction; for conditions with more persistent symptoms, a non-sedating antihistamine should be used regularly.

An oral antihistamine may be used to prevent urticaria, and for the treatment of acute urticarial rashes, pruritus, insect bites, and stings. Antihistamines are also used in the management of anaphylaxis and angioedema, of nausea and vomiting, and of migraine.

Oral antihistamines are also used in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hay fever), and may be of some value in vasomotor rhinitis; rhinorrhea and sneezing is reduced, but antihistamines are usually less effective for nasal congestion. Antihistamines are used topically to treat allergic reactions in the eye and in the nose. Topical application of antihistamines to the skin is not recommended.

Sedating antihistamines
Used in allergic disorders, motion sickness, vertigo, itch associated with skin disorders, nausea, and for sedation including premedication. They commonly have anticholinergic and CNS adverse effects (drowsiness). Many are short acting but some, eg promethazine, act for up to 12 hours. Sedating antihistamines are occasionally useful when insomn ia is associated with urticaria and pruritus.

Less sedating antihistamines
Used only for allergic disorders. They penetrate the blood–brain barrier poorly and so have a reduced incidence of sedation; anticholinergic adverse effects are reduced due to poor affinity for muscarinic receptors. They have similar efficacy to the sedating antihistamines but are often better tolerated. Most are long acting and can be taken once daily.

Cautions and contra-indications
Antihistamines should be used with caution in hepatic impairment, and the dose may need to be reduced in renal impairment; also, use with caution in children with epilepsy. Most antihistamines should be avoided in porphyria, but some (e.g. chlorphenamine and cetirizine) are thought to be safe. Sedating antihistamines should not be given to children under 2 years, except on specialist advice, because the safety of such use has not been established. Sedating antihistamines have significant antimuscarinic activity: they should not be used in neonates and should be used with caution in children with urinary retention, glaucoma, or pyloroduodenal obstruction. Sedating antihistamines should be avoided in patients with severe liver disease: increased risk of coma.
Pregnancy and breast-feeding

No evidence of teratogenicity associated with the use of antihistamines, except for hydroxyzine and loratadine where embryotoxicity has been reported with high doses in animal studies. However, manufacturers of some antihistamines advise avoiding use during pregnancy. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates. Significant amounts of some antihistamines are present in breast milk; although not known to be harmful; manufacturers advise avoiding use in mothers who are breast-feeding.

Side-effects
Side-effects such as headache, psychomotor impairment, antimuscarinic effects (urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances) occur more commonly with the sedating antihistamines. Sedating antihistamines cause significant drowsiness, but paradoxical stimulation may occur rarely especially with high doses. Other side-effects common to all antihistamines include palpitation, hypotension, hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis, rashes and photosensitivity reactions), extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, blood disorders, and liver dysfunction.

03.04.01 Sedating Antihistamines

CHLORPHENAMINE
DEXCHLORPHENIRAMINE

Dexchlorpheniramine is the dextroisomer of chlorpheniramine.

Mode of action
Antagonise the action of histamine at H1 receptors, reducing histamine-related vasodilation and increased capillary permeability.
They also have anticholinergic activity, some have alpha-blocking activity and some have antiserotonin activity.

Indications
Allergic upper respiratory and dermatological conditions including rhinitis, conjunctivitis, urticaria, pruritis and contact dermatitis.
Nausea and vomiting.
Sedation, eg premedication.

Specific considerations
Closed angle glaucoma, increased intraocular pressure, pyloroduodenal obstruction, bladder neck obstruction, hyperthyroidism: may be exacerbated by the anticholinergic effects of antihistamines.
Elderly: Lower dose may be required; elderly are at greater risk of adverse effects, eg dizziness, sedation, confusion, hypotension and falls.
Recommendations for the minimum age at which children can receive these drugs range from 2–3 years.
Pregnancy: Safe to use; ADEC category A.
Lactation: Safe to use.

Adverse effects
Common: sedation, dizziness, tinnitus, blurred vision, euphoria, incoordination, anxiety, insomnia, tremor, nausea, vomiting, constipation, diarrhoea, epigastric discomfort, dry mouth, cough.
Infrequent: urinary retention, palpitations, hypotension, headache, hallucination, psychosis.
Rare: leucopenia, agranulocytosis, haemolytic anaemia, allergic reactions, arrhythmias, dyskinesia, seizures, paraesthesia, paralysis, hepatitis.
Paradoxical stimulation: CNS stimulation may occur rarely, especially in children (excitation, hallucinations, ataxia, seizures), rather than sedation.

Dosage
Adult, child >12 years: Controlled release tablet, 6 mg twice daily. Conventional tablet, 2 mg 4 times daily.
Child 6–12 years: Conventional tablet, 1 mg 4 times daily.
Child 2–6 years: Oral liquid, 0.04 mg/kg/dose 3 times daily.

Patient counseling
These medications may make you sleepy; don't drive or operate machinery if this happens.
Avoid alcohol and other medication which may cause sedation.

Practice points
- also available in a combination preparation with pseudoephedrine; there is little rationale for this preparation; avoid use
antihistamines should be stopped about 4 days before skin-prick testing
some antihistamines are available with decongestants and/or analgesics for relief of pain, cough, nasal congestion or symptoms of influenza, the common cold and allergies; there is little rationale for these combinations; avoid use
avoid use of antihistamines for the symptomatic treatment of upper respiratory tract infections in young children because of the self-limiting nature of the illness and lack of demonstrated benefit.

Products
CHLORPHENAMINE SYRUP 2-2.5 MG/5ML (AS MALEATE)  100-120 ML BOTTLE (ALLERFIN®, HISTANORE®, ISTAMEX®)
CHLORPHENIRAMINE AMPS 10 MG/AMP (AS MALEATE)  2 ML AMP (ALLERFIN®)
CHLORPHENIRAMINE TABS 4 MG (AS MALEATE) (ALLERFIN®, CHLORPHENIRAMINE®)

HYDROXYZINE
Mode of action
Hydroxyzine, a piperazine derivative, is a sedating antihistamine (antagonise the action of histamine at H1 receptors), it has antimuscarinic and antiemetic effect.
Indications
Pruritis, urticaria, anxiety (short term), premedication, adjunct to opioid analgesia in the management of cancer pain.
Adverse Effects and Precautions
As for the sedating antihistamines in general,
Arrhythmias: ECG abnormalities, particularly alterations in T-waves, were associated with anxiolytic doses of hydroxyzine hydrochloride and were similar to those produced by thioridazine and tricyclic antidepressants.
Porphyria: Hydroxyzine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.
Patient counselling
These medications make some people sleepy; don’t drive or operate machinery if this occurs.

Products
HYDROXYZINE TABS 25 MG (AS HCL) (ATARAX®)

PROMETHAZINE
Phenothiazine
Mode of action
Antagonise the action of histamine at H1 receptors, reducing histamine-related vasodilation and increased capillary permeability.
They also have anticholinergic activity, some have alpha-blocking activity and some have antiserotonin activity.
Indications
Allergic upper respiratory and dermatological conditions including rhinitis, conjunctivitis, urticaria, pruritis and contact dermatitis.
Anaphylactic and anaphylactoid reactions, adjunct for treatment and prophylaxis.
Nausea and vomiting, including motion sickness.
Sedation, eg for cases of burns, measles, chickenpox. premedication
Specific considerations
Phenylketonuria: avoid use of Gold Cross Antihistamine Elixir®; contains aspartame.
Sulfite allergy: avoid use of some oral liquid and injection brands, contain sodium metabisulfite.
Epilepsy: lowers the seizure threshold.
Respiratory depression: may exacerbate respiratory depression.
Closed angle glaucoma, increased intraocular pressure, pyloroduodenal obstruction, bladder neck obstruction, hyperthyroidism: may be exacerbated by the anticholinergic effects of antihistamines.
Elderly: Lower dose may be required; elderly are at greater risk of adverse effects, eg dizziness, sedation, confusion, hypotension and falls.
Children: Epidemiologic studies have found an increased incidence of use of phenothiazine antihistamines (promethazine, trimetrazine, methdilazine) in infants with sudden infant death syndrome (SIDS) and near miss SIDS than in a control group. Avoid phenothiazine antihistamines in young children. Recommendations for the minimum age at which children can receive these drugs range from 2–3 years.
Pregnancy: Safe to use for nausea and vomiting in early pregnancy; theoretical risk of neurological disturbance in infants when taken in late pregnancy; ADEC category C.
Breastfeeding: May sedate mother; short term use is unlikely to be of concern.

**Adverse effects**
Common: sedation, dizziness, tinnitus, blurred vision, euphoria, incoordination, anxiety, insomnia, tremor, nausea, vomiting, constipation, diarrhoea, epigastric discomfort, dry mouth, cough.
Infrequent: urinary retention, palpitations, hypotension, headache, hallucination, psychosis, thrombophlebitis.
Rare: leucopenia, agranulocytosis, haemolytic anaemia, allergic reactions, arrhythmias, dyskinesia, seizures, paraesthesia, paralysis, hepatitis.
Paradoxical stimulation: CNS stimulation may occur rarely, especially in children (excitation, hallucinations, ataxia, seizures), rather than sedation.

**Dosage**
Adult: Allergic disorder, sedation, oral 25–75 mg once daily, or 10–25 mg 2–3 times daily; or IM 25–50 mg.
Premedication, IM 25–50 mg 1–2 hours before procedure.
Child >2 years: Sedation, IM/oral 0.5 mg/kg, single dose.
Allergy, IM/oral 0.125 mg/kg 3 times daily, and 0.5 mg/kg at night.
Anaphylaxis, IM/oral 1 mg/kg up to 25–50 mg.

**Patient counselling**
These medications may make you sleepy; don't drive or operate machinery if this happens.
Avoid alcohol and other medication which may cause sedation.

**Practice points**
- promethazine is available as 2 different salt forms: promethazine hydrochloride has greater potency than promethazine theoclate; 1 mg promethazine hydrochloride is equivalent to 1.5 mg promethazine theoclate.
- Promethazine theoclate is only marketed for motion sickness and nausea and vomiting
- antihistamines should be stopped about 4 days before skin-prick testing
- some antihistamines are available with decongestants and/or analgesics for relief of pain, cough, nasal congestion or symptoms of influenza, the common cold and allergies; there is little rationale for these combinations; avoid use
- avoid use of antihistamines for the symptomatic treatment of upper respiratory tract infections in young children because of the self-limiting nature of the illness and lack of demonstrated benefit.

**Products**
PROMETHAZIN ELIXER 5 MG/5ML (AS HCL) 100 ML BOTTLE (HISTAZIN®)
PROMETHAZIN TABS 25 MG (AS HCL) (HISTAZIN®, PROMET®)

### 03.04.02 Less Sedating Antihistamines

**CETIRIZINE**

**Mode of action**
Selectively antagonise the action of histamine at H1 receptors. Histamine release causes vasodilation and increases capillary permeability.

**Indications**
Allergic rhinitis and conjunctivitis, Chronic urticaria.

**Contraindications**
Allergy to cetirizine.

**Specific considerations**
Renal impairment: Reduce dose in moderate-to-severe impairment.
Pregnancy: Used to treat symptoms of cholestasis of pregnancy; ADEC category B2.
Elderly: Increased risk of sedation and anticholinergic effects; monitor carefully.
Children: Avoid use in children <2 years.
Pregnancy: More experience with older sedating antihistamines.
Breastfeeding: Safe to use.

**Adverse effects**
Common: drowsiness, fatigue, headache, nausea, dry mouth.
Infrequent: elevated liver enzymes, weight gain.
Rare: rash, hypersensitivity (eg anaphylaxis, bronchospasm).

**Dosage**
Adult: Initially, 10 mg once daily; maximum 20 mg once daily.
Child
6–12 years, 5 mg twice daily.
2–6 years, 2.5–5 mg daily or 2.5 mg twice daily.
1–2 years, 0.125 mg/kg twice daily.
Renal impairment: Moderate impairment, give half dose.
Severe impairment, give quarter dose.

**Patient counseling**
Avoid drinking alcohol while taking this medicine
These medications make some people sleepy; don't drive or operate machinery if this occurs.

**Practice points**
- most likely of the less sedating antihistamines to cause sedation
- antihistamines should be stopped at least 4 days before skin-prick testing.

**Products**
- CETIRIZINE SYRUP 5 MG/5ML (AS HCL) 100-200 ML BOTTLE (CERIN®, FINALLERG®, ZYRTEC®)
- CETIRIZINE TABS 10 MG (AS HCL) (CERIN®, CETOLERG®, FINALLERG®, ZERAN®, ZYRTEC®)

**LORATADINE**

**Mode of action**
Selectively antagonise the action of histamine at H1 receptors. Histamine release causes vasodilation and increases capillary permeability.

**Indications**
Allergic rhinitis and conjunctivitis, Chronic urticaria, Allergic rhinitis and conjunctivitis, Chronic urticaria.

**Contraindications**
Allergy to loratadine or desloratadine.

**Specific considerations**
Pre-existing QT prolongation: may increase risk of serious ventricular arrhythmia (1 case report).
Hepatic impairment: Reduce starting dose in severe impairment.
Pregnancy: Used when a sedating antihistamine is unacceptable; ADEC category B1.
Elderly: Increased risk of sedation and anticholinergic effects particularly with cetirizine and loratadine; monitor carefully.
Children: Avoid use in children <2 years.
Pregnancy: More experience with older sedating antihistamines.
Lactation: Safe to use.

**Adverse effects**
Common: drowsiness, fatigue, headache, nausea, dry mouth.
Infrequent: elevated liver enzymes, weight gain.
Rare: rash, hypersensitivity (eg anaphylaxis, bronchospasm).

**Dosage**
- Adult, child >30 kg: 10 mg once daily.
- Child 2–12 years, <30 kg: 5 mg once daily.
- Child 1–2 years: 2.5 mg once daily.
Severe hepatic impairment: Adult, initially 5 mg daily.

**Patient counselling**
These medications make some people sleepy; don't drive or operate machinery if this occurs.

**Practice points**
- loratadine is also available in combination preparations with pseudoephedrine; there is little rationale for these preparations; avoid use
- antihistamines should be stopped at least 4 days before skin-prick testing.

**Products**
- LORATADINE SYRUP 5 MG/5ML 100 ML BOTTLE (CLARITINE®, LORMINE®, HISTAL®, LORINE®, KLARIHIST®, LARIDON®, LORATAN®, LOREEN®, RAMITIN®, RESTAMINE®, TIDILOR®)
- LORATADINE TABS 10 MG (ALARIN®, CLARITINE®, HISTAL®, LORINE®, KLARIHIST®, LARIDON®, LORATAN®, LOREEN®, RAMITIN®, RESTAMINE®, TIDILOR®, RAYON®)

**FEXOFENADINE**

**Mode of action**
Selectively antagonise the action of histamine at H1 receptors. Histamine release causes vasodilation and increases
capillary permeability.

**Indications**
Allergic rhinitis and conjunctivitis, Chronic urticaria.

**Contraindications**
Allergy to fexofenadine.

**Specific considerations**
Pre-existing QT prolongation: may increase risk of serious ventricular arrhythmia (1 case report).
Renal impairment: Reduce dose in severe impairment.
Pregnancy: Avoid use; ADEC category B2.
Elderly: Increased risk of sedation and anticholinergic effects; monitor carefully.
Children: Avoid use in children <2 years.
Pregnancy: More experience with older sedating antihistamines.
Breastfeeding: Safe to use.

**Adverse effects**
Common: drowsiness, fatigue, headache, nausea, dry mouth.
Infrequent: elevated liver enzymes, weight gain.
Rare: rash, hypersensitivity (eg anaphylaxis, bronchospasm).

**Dosage**
Rhinitis: Adult, child >12 years, 120 mg daily in 1 or 2 divided doses.
Urticaria: Adult, child >12 years, 180 mg once daily.
Severe renal impairment: 60 mg daily.
Child 6–11 years: 30 mg twice daily.

**Patient counselling**
These medications make some people sleepy; don't drive or operate machinery if this occurs.

**Practice points**
- antihistamines should be stopped at least 4 days before skin-prick testing.

**Products**
FEXOFENADINE TABS 120 MG (AS HCL) (FENADEX®, FEXADINE®, TELFAST®)
FEXOFENADINE TABS 180 MG (AS HCL) (TELFAST®)

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**03.05. PULMONARY SURFACTANT**

**Mode of action**
Restore lung surface tension by acting as substitutes for human pulmonary surfactant.

**Indications**
Treatment and prevention of respiratory distress syndrome (RDS) in preterm infants.

**Adverse effects**
During administration transient bradycardia and decreased oxygen saturation are common while transient endotracheal tube obstruction and hypotension occur infrequently.
Rare: pulmonary haemorrhage (particularly in very premature infants).

**Comparative information**
Beractant is of bovine origin and poractant alfa is of porcine origin.
They appear to have a similar safety profile.
Limited data suggest poractant alfa improves oxygenation more rapidly than beractant when used to treat RDS.

**Practice points**
- surfactants can be used to treat established RDS (rescue treatment) or as preventive treatment (administered shortly after birth to infants considered to be at significant risk of developing RDS)
- preventive or rescue treatment with surfactant reduces mortality and morbidity of preterm infants (<32 weeks gestation) with RDS: preventive treatment is more effective than rescue treatment
- antenatal corticosteroid administration remains first line treatment for prevention of RDS.

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**BERACTANT**

**Mode of action**
Restore lung surface tension by acting as substitutes for human pulmonary surfactant.

**Indications**
Treatment and prevention of respiratory distress syndrome in preterm infants.
Adverse effects
During administration transient bradycardia and decreased oxygen saturation are common while transient endotracheal tube obstruction and hypotension occur infrequently.
Rare: pulmonary haemorrhage (particularly in very premature infants).

Dosage
Intratracheal 4 mL/kg; may be repeated up to 4 times in 48 hours at intervals of at least 6 hours.
Practice points: same as class

Products
BERACTANT INTRATRACHEAL 100 MG/ML 4 ML VIAL (SURVANTA®)

03.06 COUGH PREPARATIONS

03.06.02 Cough suppressants
The drawbacks of prescribing cough suppressants are rarely outweighed by the benefits of treatment and only occasionally are they useful. As, for an example, if sleep is disturbed by a dry cough. Cough suppressants may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.
Opioid cough suppressants such as Codeine, Dextromethorphan, and pholcodeine are seldom sufficiently potent to be effective in severe cough; all tend to cause constipation.
Sedative antihistamines, such as Diphenhydramine, are used as the cough suppressant component of many compound cough preparations on sale to the public: all tend to cause drowsiness which may reflect their main mode of action.

CODEINE
Opioid
Mode of action
Opioid derivatives; they depress the medullary cough centre.

Indications
Symptom relief in non-productive cough.

Contraindications
Respiratory failure, asthma, COPD

Specific considerations
Renal impairment: Increased and prolonged effect; reduce dosage in moderate-to-severe impairment.
Elderly: May require reduction in dosage.
Children: Do not use in children <2 years.
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: No data available but should be safe to use.

Adverse effects
Common: drowsiness, constipation, nausea, vomiting.
Rare: respiratory depression.

Dosage
Adult: 15–30 mg 3–4 times daily.
Child: >2 years, 0.25–0.5 mg/kg/dose every 6–8 hours.

Patient counseling
This medication may make you drowsy; do not drive or operate machinery if you are affected.
Avoid taking alcohol as it may increase the feeling of drowsiness.

Practice points
- avoid use in productive cough

Products
Codein powder

DEXTROMETHORPHAN
Opioid
Mode of action
Opioid derivatives; they depress the medullary cough centre.

Indications
Symptom relief in non-productive cough.
**Contraindications**
Manufacturers contraindicate use with, or within 14 days of, a MAOI
Respiratory failure, asthma, COPD.

**Specific considerations**
- Treatment with drugs which can contribute to the serotonin syndrome: increases the likelihood of serotonin syndrome; avoid combinations or monitor clinical course carefully.
- Renal impairment: Increased and prolonged effect; reduce dosage in moderate-to-severe impairment.
- Hepatic impairment: May require reduction in dosage.
- Elderly: May require reduction in dosage.
- Children: Do not use in children <2 years.
- Pregnancy: Safe to use; ADEC category A.
- Breastfeeding: No data available but should be safe to use.

**Adverse effects**
- Common: drowsiness, constipation, nausea, vomiting.
- Rare: respiratory depression.

**Dosage**
- Adult: 10–20 mg 3–4 times daily.
- Child: 2–5 years, 2.5–5 mg 3–4 times daily; >5 years, 5–10 mg 3–4 times daily.

**Patient counseling**
- This medication may make you drowsy; do not drive or operate machinery if you are affected.
- Avoid taking alcohol as it may increase the feeling of drowsiness.

**Practice points**
- Avoid use in productive cough

**Products**
**Assorted cough mixtures**

**DIHYDROCODEINE**
Opioid

**Mode of action**
Opioid derivatives; they depress the medullary cough centre.

**Indications**
Symptom relief in non-productive cough.

**Contraindications**
Respiratory failure, asthma, COPD.

**Specific considerations**
- Renal impairment: Increased and prolonged effect; reduce dosage in moderate-to-severe impairment.
- Hepatic impairment: May require reduction in dosage.
- Elderly: May require reduction in dosage.
- Children: Do not use in children <2 years.
- Pregnancy: Safe to use; ADEC category A.
- Breastfeeding: No data available but should be safe to use.

**Adverse effects**
- Common: drowsiness, constipation, nausea, vomiting.
- Rare: respiratory depression.

**Dosage**
- Adult: 10–20 mg 3–4 times daily.
- Child: 2–5 years, 1.25–2.5 mL/dose up to 6 times daily; >5 years, 2.5–5 mL/dose up to 6 times daily.

**Patient counseling**
- This medication may make you drowsy; do not drive or operate machinery if you are affected.
- Avoid taking alcohol as it may increase the feeling of drowsiness.

**Practice points**
- Avoid use in productive cough

**Products**
**DIHYDROCODEINE TABS 60 MG (AS TARTARATE) (DHC CONT®)**
Other Combinations
COUGH MIXTURE WITH CODEINE SYRUP 100-120 ML BOTTLE (TRIFED COMPOUND®, TUSSIFIN WITH CODEIN®)

04.05.02 MUCOLYTICS

BROMHEXINE
Mode of action
Reduces mucus viscosity.
Indications
Adjuvant treatment in bronchopulmonary disease with excessive or viscous mucus.
Specific considerations
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: No data available but should be safe to use.
Adverse effects
nausea, diarrhea.
Dosage
Adult: 8–16 mg 3 times daily.
Child: 1–3 years, 4 mg 3 times daily, >3 years, 8 mg 3 times daily.
Products
BROMHEXINE SYRUP/ELIXER 4 MG/5ML (AS HCL) 100 ML BOTTLE (BISOLVON®, BRONCHOTUSSINE®, EXOLIT®, MUCOFREE®, MUCOLYTE®, RIAXINE®, SOLVEXIN®)

04.05.03 Expectorants
Products
COUGH MIXTURE WITHOUT CODEINE SYRUP 120 ML BOTTLE (COFFEX®, COLFED EXPECTORANT®, JOSWE NO-CUF®, TRIFED EXPECTORANT®, TUSSITOP®, UNIFED EXPECTORANT®)

04.07 ORAL SYMPATHOMIMETIC DECONGESTANTS

PSEUDOEPHEDRINE
Mode of action
Act on alpha adrenoreceptors on vascular smooth muscle in the respiratory tract, producing vasoconstriction of dilated nasal vessels, reducing tissue swelling and nasal congestion.
Indications
Relief of nasal congestion associated with acute and chronic rhinitis.
Contraindications
Severe or uncontrolled hypertension, or severe coronary artery disease, MAOI treatment.
Specific considerations
Diabetes: may affect blood glucose control.
Heart disease: increased risk of arrhythmias.
Hypertension: BP may increase.
Prostatic hypertrophy: symptoms may be exacerbated.
Hyperthyroidism: increases sensitivity to sympathomimetics.
Closed angle glaucoma: may induce acute attack.
Elderly: Use lowest effective dose as the elderly are particularly susceptible to adverse effects.
Children: Avoid use in children <2 years.
Pregnancy: Avoid use, particularly in the first trimester; ADEC category B2.
Breastfeeding: Safe to use.
Adverse effects
Common: CNS stimulation, nervousness, excitability, dizziness, insomnia.
Infrequent: tachycardia, palpitations.
Rare: hallucination (particularly in children) arrhythmias, seizures, hypertension, ischaemic colitis.
Dosage
Pseudoephedrine is included in many over-the-counter preparations; dosage may depend on the type of combination used, or whether it is controlled release.
Adult, 60 mg every 4–6 hours; maximum 240 mg daily. Controlled release tablets, 120 mg every 12 hours.
Child >2 years, 1 mg/kg 3–4 times daily.

Practice points
• oral decongestants are less effective than intranasal agents, but do not cause rebound nasal congestion
• oral decongestants are included in many over-the-counter preparations for the symptomatic relief of nasal obstruction associated with the common cold
• do not use controlled release products in children
• potential for misuse by people dependent on stimulants or wanting to reformulate products for illegal sale: tighter control on the sale of products containing pseudoephedrine now exist

Products
PSEUDOEPHEDRINE+CETIRIZINE CAPS 120 MG+5 MG (AS HCL) (CIRRUS®)
PSEUDOEPHEDRINE+DEXTROMETHORPHAN+CHLOROPHENIRAMINE SYRUP
30+10+1.25MG/5ML  120 ML BOTTLE (COLFED DM®, UNIFED DM®)
PSEUDOEPHEDRINE+TRIPROLIDINE SYRUP 30+1.25 MG/5ML (AS HCL)  120 ML BOTTLE
(COLFED®, TRIFED®, UNIFED®)
PSEUDOEPHEDRINE+TRIPROLIDINE TABS 60+2.5MG (AS HCL) (TRIFED®, UNIFED®)
### Table 03-01 Stepwise maintenance management of asthma in adults

<table>
<thead>
<tr>
<th>Intermittent asthma</th>
<th>Mild persistent asthma</th>
<th>Moderate persistent asthma</th>
<th>Severe persistent asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>inhaled short acting beta₂ agonist as required&lt;sup&gt;1&lt;/sup&gt;</td>
<td>inhaled short acting beta₂ agonist as required&lt;sup&gt;2&lt;/sup&gt; AND low dose inhaled corticosteroid&lt;sup&gt;3&lt;/sup&gt; OR cromoglycate&lt;sup&gt;4&lt;/sup&gt; OR nedocromil&lt;sup&gt;4&lt;/sup&gt;</td>
<td>inhaled short acting beta₂ agonist as required&lt;sup&gt;2&lt;/sup&gt; AND medium dose inhaled corticosteroid&lt;sup&gt;5&lt;/sup&gt; OR long acting beta₂ agonist combined with inhaled corticosteroid&lt;sup&gt;6&lt;/sup&gt;</td>
<td>inhaled short acting beta₂ agonist as required&lt;sup&gt;2&lt;/sup&gt; AND high dose inhaled corticosteroid OR long acting beta₂ agonist with inhaled corticosteroid&lt;sup&gt;6&lt;/sup&gt; consider adding leukotriene-receptor antagonist OR theophylline CR ADD oral corticosteroid when required</td>
</tr>
</tbody>
</table>

<sup>1</sup>add preventive treatment if short acting beta₂ agonist is required <sup>3</sup> or more times a week

<sup>2</sup>use of short acting beta₂ agonist >2 inhalations 2–3 times daily indicates loss of asthma control; increase dose of inhaled corticosteroid or add a long acting beta₂ agonist if the patient is already taking an appropriate dose of inhaled corticosteroid

<sup>3</sup><400 micrograms budesonide or <200–250 micrograms HFA-beclomethasone or fluticasone daily

<sup>4</sup>if a 4-week therapeutic trial is not effective, use inhaled corticosteroid

<sup>5</sup><800–1000 micrograms budesonide or <400–500 micrograms HFA-beclomethasone or fluticasone daily

<sup>6</sup>if control not achieved with 400 micrograms budesonide or 200–250 micrograms HFA-beclomethasone or fluticasone daily

<sup>7</sup><2000 micrograms budesonide or <1000 micrograms HFA-beclomethasone or fluticasone daily

### Table 03-02 Stepwise maintenance management of asthma in children

<table>
<thead>
<tr>
<th>Infrequent episodic asthma (episodes &gt;6–8 weeks apart)</th>
<th>Frequent episodic asthma (episodes &lt;6 weeks apart)</th>
<th>Persistent asthma (symptoms most days, nocturnal asthma more than once a week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>inhaled short acting beta₂ agonist as required</td>
<td>inhaled short acting beta₂ agonist as required AND inhaled corticosteroid (minimum effective dose) OR cromoglycate&lt;sup&gt;1&lt;/sup&gt; OR nedocromil&lt;sup&gt;1&lt;/sup&gt; OR leukotriene-receptor antagonists&lt;sup&gt;1&lt;/sup&gt;</td>
<td>inhaled short acting beta₂ agonist as required AND inhaled corticosteroid (minimum effective dose) consider adding long acting beta₂ agonist if required add theophylline CR ADD oral corticosteroid when required</td>
</tr>
</tbody>
</table>

<sup>1</sup>if a 4-week therapeutic trial is not effective, use inhaled corticosteroid
CHAPTER 04 CENTRAL NERVOUS SYSTEM

04.01 HYPNOTICS AND ANXIOLYTICS

INSOMNIA
Non-drug treatments are first line. Useful self management strategies include relaxation techniques and sleep hygiene principles. Cognitive therapy, light therapy and other techniques may also be successful; seek specialist advice from a sleep disorders unit.
Limit use of benzodiazepines or related drugs to the shortest time possible and agree to a definite time limit with the person.
There is no convincing evidence for significant differences in efficacy or safety of agents such as zopiclone and zolpidem compared with benzodiazepines for insomnia.
Many other agents, with and without approved indications for insomnia, are used in managing sleep disturbance. Use of TCAs, sedating antihistamines (e.g. diphenhydramine, promethazine, doxylamine), or antipsychotics to manage insomnia is not recommended due to their toxicity and/or risk of adverse effects, and limited evidence for effectiveness.
Valerian is a complementary medicine promoted for improving sleep, based on limited data showing small benefit.

04.01.01 Hypnotics

ALPRAZOLAM
Mode of action
Benzodiazepines potentiate the inhibitory effects of gamma-aminobutyric acid (GABA) throughout the CNS, resulting in anxiolytic, sedative, hypnotic, muscle relaxant and antiepileptic effects.
Indications
Anxiety, including anxiety with symptoms of depression, Panic disorder, Insomnia, Parasomnias (night terrors, sleepwalking), Epilepsy, seizures, Acute behavioural disturbance, Acute alcohol, barbiturate and benzodiazepine withdrawal, Muscle spasm, Premedication, Sedation for procedures and in intensive care units, Restless legs syndrome.
Contraindications
Respiratory depression.
Severe hepatic impairment, particularly when hepatic encephalopathy is present.
Myasthenia gravis.
Specific considerations
Respiratory disease, sleep apnoea: compromised respiratory drive may result in hypoventilation and hypoxaemia.
Muscle weakness: risk of exacerbation.
Renal impairment: Increased sensitivity to CNS effects; use a lower initial dose in severe impairment.
Hepatic impairment: Can precipitate coma; low doses of a short acting agent are preferable.
Elderly: Use low doses of a short or medium acting agent; increased risk of oversedation, ataxia, confusion, falls, respiratory depression and short term memory impairment.
Children: Avoid, except short term in specific conditions (e.g. night terrors, sleepwalking); greater sensitivity to CNS effects.
Pregnancy: Avoid if possible, particularly large doses and regular use (risk of growth retardation and neonatal withdrawal syndrome). Administration of high doses before or during labour may cause respiratory depression, hypothermia and floppy infant syndrome (hypotonia, lethargy and poor suckling). If used during pregnancy short acting drugs are preferable to long acting; plan to stop gradually before delivery; ADEC category C
Breastfeeding: Avoid repeated doses; may cause lethargy and weight loss in the infant.
Adverse effects
Common: drowsiness, oversedation, light-headedness, memory loss, hypersalivation, ataxia, slurred speech.
Infrequent: headache, vertigo, disorientation, confusion, paradoxical excitation, euphoria, aggression and hostility, anxiety, decreased libido, anterograde amnesia, respiratory depression, hypotension IV injection, pain and thrombophlebitis, severe hypotension, arrhythmias, respiratory arrest.
Rare: blood disorders, including leucopenia and leucocytosis, jaundice, transient elevated liver function tests, allergic reactions, including rash and anaphylaxis.
Dosage
Anxiety: Initially 0.25–0.5 mg 3 times daily. Range, 0.5–4 mg daily.
Panic disorder: Initially 0.5–1 mg at night, increased by 0.25–1 mg every 3 days until symptoms are controlled.
Maximum, 10 mg daily.
Elderly and/or debilitated patient: Initially 0.25 mg 2–3 times daily.

**Patient Counseling**
You may feel drowsy while taking this medication; drowsiness may persist the following day; avoid driving or operating heavy equipment until you know how you react.
Avoid alcohol and other medications that may cause drowsiness while taking this drug.
If you take this medicine regularly for more than 2–4 weeks your body may become used to it and in time, you may need a higher dose for it to continue to work. If you stop the medicine suddenly, you may have unpleasant effects (e.g. feeling anxious, difficulty sleeping). Discuss how to stop the medicine with your doctor first.

**Practice points**
- Although some evidence suggests that alprazolam may be effective for mild depressive illness and premenstrual dysphoria, antidepressant treatments are preferred, particularly in the longer term
- There is no convincing evidence for the use of benzodiazepines to treat depression, but they are appropriately used short term to treat severe anxiety or agitation in depressed people waiting for response to antidepressants
- Benzodiazepines are sometimes misused for their euphoric and sedative effects, both alone and with other drugs
- Reserve for short term use only (e.g. 2–4 weeks); they should be part of a broader treatment plan, not a sole treatment
- Long term use of benzodiazepines may result in tolerance and dependence; signs of dependence include drug-seeking behaviour, craving, and disturbed work and personal function
- Sudden stopping treatment in dependent people may produce withdrawal symptoms, including anxiety, dysphoria, irritability, insomnia, nightmares, sweating, memory impairment, hallucinations, hypertension, tachycardia, psychosis, tremors and seizures
- Withdrawal symptoms may not occur until several days after stopping, and can last for several weeks or longer after prolonged use; prevent or alleviate by gradual dose reduction.

**Products**
ALPRAZOLAM TABS 0.5 MG (ALPRANAX®, APO-ALPRAZ®, PRAZIN®, PROZINE®, XANAX®, ZOLAM®)

ZOLPIDEM
Non-benzodiazepine hypnotic

**Mode of action**
Potentiation of inhibitory effects of gamma-aminobutyric acid (GABA).

**Indications**
Short term treatment of insomnia

**Contraindications**
Myasthenia gravis, Acute or severe pulmonary insufficiency

**Specific considerations**
Hepatic impairment: Use low doses.
Elderly: Use low doses.
Children: Efficacy and safety are not established in people <18 years.
Pregnancy: Contact specialised information service
Breastfeeding: Contact specialised information service.

**Adverse effects:**
Common: diarrhoea
Infrequent: hallucinations
Rare: amnesia

**Dosage**
Adult: 5–10 mg immediately before bedtime.
Elderly or hepatic impairment: 5 mg immediately before bedtime.

**Practice points**
- potential for dependence, tolerance or misuse is not clear; use short term
04.01.02 Anxiolytics

**BENZODIAZEPINES (BROMAZEPAM, DIAZEPAM, LORAZEPAM)**

**Mode of action**
Benzodiazepines potentiate the inhibitory effects of gamma-aminobutyric acid (GABA) throughout the CNS, resulting in anxiolytic, sedative, hypnotic, muscle relaxant and antiepileptic effects.

**Indications**
Anxiety, Panic disorder, Insomnia, Parasomnias (night terrors, sleepwalking), Epilepsy, seizures, behavioural disturbance. Acute alcohol, barbiturate and benzodiazepine withdrawal, Muscle spasm, Premedication, sedation for procedures and in intensive care units, Restless legs syndrome.

**Contraindications**
Respiratory depression, Severe hepatic impairment, particularly when hepatic encephalopathy is present, Myasthenia gravis.

**Specific considerations**
Respiratory disease, sleep apnoea: compromised respiratory drive may result in hypoventilation and hypoxaemia.
Muscle weakness: risk of exacerbation.
Renal impairment: Increased sensitivity to CNS effects; use a lower initial dose in severe impairment.
Hepatic impairment: Can precipitate coma; low doses of a short acting agent are preferable.
Elderly: Use low doses of a short or medium acting agent; increased risk of oversedation, ataxia, confusion, falls, respiratory depression and short term memory impairment.
Children: Avoid, except short term in specific conditions (e.g. night terrors, sleepwalking); greater sensitivity to CNS effects.
Pregnancy: Avoid if possible, particularly large doses and regular use (risk of growth retardation and neonatal withdrawal syndrome). Administration of high doses before or during labour may cause respiratory depression, hypothermia and floppy infant syndrome (hypotonia, lethargy and poor suckling). If used during pregnancy short acting drugs are preferable to long acting; plan to stop gradually before delivery; ADEC category C.
Breastfeeding: Avoid repeated doses; may cause lethargy and weight loss in the infant.

**Adverse effects**
Common: drowsiness, oversedation, light-headedness, memory loss, hypersalivation, ataxia, slurred speech.
Infrequent: headache, vertigo, disorientation, confusion, paradoxical excitation, euphoria, aggression and hostility, anxiety, decreased libido, anterograde amnesia, respiratory depression, hypotension.
IV injection—pain and thrombophlebitis, severe hypotension, arrhythmias, respiratory arrest.
Rare: blood disorders, including leucopenia and leucocytosis, jaundice, transient elevated liver function tests, allergic reactions, including rash and anaphylaxis.

**Comparative information**
Very short acting (half-life <6 hours)—midazolam, triazolam.
Short acting (half-life 6–12 hours)—alprazolam, oxazepam, temazepam.
Medium acting (half-life 12–24 hours)—lorazepam, bromazepam.
Long acting (half-life >24 hours)—clobazam, clonazepam, diazepam, flunitrazepam, nitrazepam.
Rapid onset (<1 hour after oral administration)—alprazolam, diazepam, flunitrazepam, midazolam, temazepam, triazolam.

Shorter acting agents (particularly those with rapid onset of action) are more likely to lead to acute withdrawal symptoms. Diazepam’s rapid onset of action and long half-life mean it is associated with less withdrawal.

Long acting agents, eg diazepam, clonazepam, are preferred when using benzodiazepines as prophylaxis against withdrawal from alcohol, barbiturates or other benzodiazepines.

**Patient counselling**
You may feel drowsy while taking this medication; drowsiness may persist the following day; avoid driving or operating heavy equipment until you know how you react.
Avoid alcohol and other medications that may cause drowsiness while taking this drug.
If you take this medicine regularly for more than 2–4 weeks your body may become used to it and in time, you may need a higher dose for it to continue to work. If you stop the medicine suddenly, you may have unpleasant effects (eg feeling anxious, difficulty sleeping). Discuss how to stop the medicine with your doctor first.

**Practice points**
- There is no convincing evidence for the use of benzodiazepines to treat depression, but they are appropriately used short term to treat severe anxiety or agitation in depressed people waiting for response to antidepressants.
- Benzodiazepines are sometimes misused for their euphoric and sedative effects, both alone and with other drugs.
- Reserve for short term use only (e.g., 2–4 weeks); they should be part of a broader treatment plan, not a sole treatment.
- Long term use of benzodiazepines may result in tolerance and dependence; signs of dependence include drug-seeking behaviour, craving, and disturbed work and personal function.
- Suddenly stopping treatment in dependent people may produce withdrawal symptoms, including anxiety, dysphoria, irritability, insomnia, nightmares, sweating, memory impairment, hallucinations, hypertension, tachycardia, psychosis, tremors, and seizures.
- Withdrawal symptoms may not occur until several days after stopping, and can last for several weeks or longer after prolonged use; prevent or alleviate by gradual dose reduction.

**BROMAZEPAM**

**Mode of Action**
Benzodiazepines potentiate the inhibitory effects of gamma-aminobutyric acid (GABA) throughout the CNS, resulting in anxiolytic, sedative, hypnotic, muscle relaxant, and antiepileptic effects.

**Indications**
- Anxiety, Panic disorder, Insomnia, Parasomnias (night terrors, sleepwalking), Epilepsy, seizures, Acute behavioural disturbance, Acute alcohol, barbiturate and benzodiazepine withdrawal, Muscle spasm, Restless legs syndrome.

**Contraindications**
- Respiratory depression.
- Severe hepatic impairment, particularly when hepatic encephalopathy is present.
- Myasthenia gravis.
- Respiratory disease, sleep apnoea: compromised respiratory drive may result in hypoventilation and hypoxaemia.
- Muscle weakness: risk of exacerbation.
- Renal impairment: Increased sensitivity to CNS effects; use a lower initial dose in severe impairment.
- Hepatic impairment: Can precipitate coma; low doses of a short-acting agent are preferable.
- Elderly: Use low doses of a short or medium-acting agent; increased risk of oversedation, ataxia, confusion, falls, respiratory depression, and short term memory impairment.
- Children: Avoid, except short term in specific conditions (e.g., night terrors, sleepwalking); greater sensitivity to CNS effects.
- Pregnancy: Avoid if possible, particularly large doses and regular use (risk of growth retardation and neonatal withdrawal syndrome). Administration of high doses before or during labour may cause respiratory depression, hypothermia, and floppy infant syndrome (hypotonia, lethargy, and poor suckling). If used during pregnancy, short-acting drugs are preferable to long acting; plan to stop gradually before delivery; ADEC category C.
- Breastfeeding: Avoid repeated doses; may cause lethargy and weight loss in the infant.

**Adverse Effects**
- Common: drowsiness, oversedation, light-headedness, memory loss, hypersalivation, ataxia, slurred speech.
- Infrequent: headache, vertigo, disorientation, confusion, paradoxical excitation, euphoria, aggression, and hostility.
- Anxiety, decreased libido, anterograde amnesia, respiratory depression, hypotension. IV injection, pain and thrombophlebitis, severe hypotension, arrhythmias, respiratory arrest.
- Rare: blood disorders, including leucopenia and leucocytosis, jaundice, transient elevated liver function tests, allergic reactions, including rash and anaphylaxis.

**Dosage**
Doses up to 6 mg can be given as a single evening dose.
- Ambulant patient: 3–6 mg 2–3 times daily.
- Elderly and/or debilitated patient: Halve normal dose.
- Severe disease, hospitalised patient: 6–12 mg 2–3 times daily.
- Maximum: 60 mg daily.
You may feel drowsy while taking this medication; drowsiness may persist the following day; avoid driving or operating heavy equipment until you know how you react.
Avoid alcohol and other medications that may cause drowsiness while taking this drug.
If you take this medicine regularly for more than 2–4 weeks your body may become used to it and in time, you may...
need a higher dose for it to continue to work. If you stop the medicine suddenly, you may have unpleasant effects (eg feeling anxious, difficulty sleeping). Discuss how to stop the medicine with your doctor first.

**Practice points**

- there is no convincing evidence for the use of benzodiazepines to treat depression, but they are appropriately used short term to treat severe anxiety or agitation in depressed people waiting for response to antidepressants
- benzodiazepines are sometimes misused for their euphoric and sedative effects, both alone and with other drugs
- reserve for short term use only (eg 2–4 weeks); they should be part of a broader treatment plan, not a sole treatment
- long term use of benzodiazepines may result in tolerance and dependence; signs of dependence include drug-seeking behaviour, craving, and disturbed work and personal function
- suddenly stopping treatment in dependent people may produce withdrawal symptoms, including anxiety, dysphoria, irritability, insomnia, nightmares, sweating, memory impairment, hallucinations, hypertension, tachycardia, psychosis, tremors and seizures
- withdrawal symptoms may not occur until several days after stopping, and can last for several weeks or longer after prolonged use; prevent or alleviate by gradual dose reduction

**Products**

**BROMAZEPAM TABS 3 MG (AKAMON®, LEXOPAM®, LEXOTANIL®, NOVEPAM®)**

**DIAZEPAM**

**Mode of action**

Same as Bromazepam

**Indications**

Marketed:

- Short term management of anxiety, agitation
- Acute alcohol withdrawal,
- Muscle spasm (see Diazepam (Neurological drugs))
- Premedication, Conscious sedation
- Status epilepticus (see Diazepam (Neurological drugs))

Accepted:

- Benzodiazepine withdrawal
- Acute behavioural disturbance
- Parasomnias (night terrors, sleepwalking)
- Panic disorder
- Insomnia
- Restless legs syndrome

**Contraindications**

Same as Bromazepam

**Specific considerations**

Same as Bromazepam

**Adverse effects**

Same as Bromazepam

**Dosage**

**Adult**

- Anxiety, agitation, parasomnias
  - Oral, 1–10 mg up to 3 times a day.
  - Suppository, 10–40 mg daily, in divided doses.
  - In anxiety, additional doses are sometimes needed.
- Premedication
  - IV, 0.1–0.2 mg/kg.
  - Suppository, 10–20 mg.
- Acute severe anxiety, agitation, behaviour disturbance
  - IV, 5–10 mg, repeated if necessary every 5–10 minutes to a maximum of 30 mg.
- Benzodiazepine withdrawal
  - Oral, give a dose equivalent to estimated total daily benzodiazepine intake in 3–4 divided doses each day at fixed
times; gradually taper dosage (eg by 10–20%) each week over several weeks. Supervision is required, eg regular review when withdrawal is undertaken as an outpatient.

Elderly and/or debilitated patient
Halve the usual adult dose.

Child
Premedication
Rectal solution/oral, 0.2–0.4 mg/kg.

Anxiety
IV, 0.1–0.3 mg/kg every 1–4 hours, up to 0.6 mg/kg in 8 hours.
Oral, 0.05–0.3 mg/kg 2–3 times daily.

Administration instructions
Give IV no faster than 5 mg/minute. Avoid extravasation, intra-arterial or IM injection.
Avoid dilution and infusion of injection (diazepam has low solubility and adsorbs to PVC giving sets).

Patient counselling
Same as Bromazepam

Practice points
- Use of diazepam for conscious sedation now less common; other agents, including midazolam, are often used in preference

Products
DIAZEPAM AMPS 5 MG/ML 2ML AMP (CALMIPAM®, DIAZEPAM®, FANIN®, STEDON®, STESOLID®, VALIUM®)
DIAZEPAM ORAL SOLUTION 2 MG/5ML 100 ML BOTTLE (CALMIPAM®)
DIAZEPAM RECTAL SOLUTION 5 MG /TUBE (STESOLID®)
DIAZEPAM RECTAL SOLUTION 10 MG/TUBE (STESOLID®)
DIAZEPAM TABS 5 MG (APO-DIAZEPAM®, CALMIPAM®, STEDON®, STESOLID® VALIUM®)

LORAZEPAM

Mode of action
Same as Bromazepam

Indications
Anxiety
Insomnia associated with anxiety
Premedication for surgery or procedure
Panic disorder
Parasomnia (night terrors, sleepwalking)
Epilepsy, seizures (see Benzodiazepines in epilepsy)
Acute behavioural disturbance
Acute alcohol, barbiturate and benzodiazepine withdrawal
Restless legs syndrome

Contraindications
Same as Bromazepam

Specific considerations
Same as Bromazepam

Adverse effects
Same as Bromazepam

Dosage
Anxiety
2–3 mg daily in divided doses. Range 1–10 mg.

Elderly and/or debilitated patient
Initially 1–2 mg daily in divided doses, adjusted as needed.
Insomnia: 1–2 mg at night.
Premedication: 2–4 mg the night before and/or 1–2 hours before the procedure.

Patient counselling
Same as Bromazepam

Practice points
Same as Bromazepam
04.01.03 Barbiturates

PHENOBARBITAL (PHENOBARBITONE)

Mode of action
Prolong inhibitory postsynaptic potential by increasing the mean chloride channel opening time and hence the duration of gamma-aminobutyric acid-induced cell membrane hyperpolarisation.

Indications
Epilepsy, including simple and complex partial seizures, generalised tonic-clonic seizures, neonatal and febrile seizures.
Status epilepticus unresponsive to benzodiazepines and phenytoin.

Contraindications
Hypersensitivity syndrome with carbamazepine, phenytoin or phenobarbitone.
Porphyria.

Specific considerations
Respiratory disease: risk of respiratory depression.
Renal impairment: May require a dose reduction.
Hepatic impairment: May require a dose reduction.
Elderly: Use with caution; increased risk of adverse effects; reduce initial dose by 30–50%.
Children: Use with caution; risk of behavioural changes and hyperactivity.

Adverse effects
Prolonged use may cause physical dependence.
Common: rash, sedation, confusion, depression, cognitive impairment, altered mood and behaviour, paradoxical insomnia, hyperactivity and aggression (particularly in children), IV, hypotension, respiratory depression.
Infrequent: nystagmus, ataxia.
Rare: exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis, megaloblastic anaemia, osteomalacia, Dupuytren's contracture, frozen shoulder, generalised pain (long term use), multi-organ hypersensitivity syndrome (including fever, severe skin disease, lymphadenopathy, haematologic abnormalities, hepatitis), IV, skin necrosis (extravasation).

Dosage
Epilepsy
Adult, oral 60–240 mg once daily at bedtime.
Child, initially, oral 3–4 mg/kg daily; up to 8 mg/kg daily may be required to achieve therapeutic plasma concentrations.
Status epilepticus: Give at rate <30 mg/minute; may be repeated after 6 hours if necessary.
Adult, IV, 10–20 mg/kg.
Child, IV, 15–20 mg/kg.

Concentration monitoring
Therapeutic range: Steady-state plasma concentration may not be achieved for 2–4 weeks:
Adult, 10–40 mg/L (45–180 micromole/L).
Child, 10–30 mg/L (45–135 micromole/L).

Patient counseling
This medicine may cause drowsiness and affect your ability to drive or operate machinery; avoid these activities until you know how it affects you.
Avoid taking alcohol as it may worsen the side effects of phenobarbitone/primidone.
This medicine interacts with many other drugs; ask your doctor or pharmacist before using any other medicine including herbal and over-the-counter products.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
- assisted ventilation is usually needed during IV injection (risk of severe respiratory depression); reduce administration rate if hypotension occurs.
- steady-state plasma concentration may not be achieved for 2–4 weeks
tolerance to sedation develops with continued administration
women taking barbiturates should use non-hormonal contraception such as copper-releasing IUD (see Contraception)

Products
PHENOBARBITAL AMPS 200 MG/AMP  1 ML AMP (NOT REGISTERED)

04.02 DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Antipsychotics (also called neuroleptics) are used primarily to treat psychotic disorders.
Rationale for use includes relief from symptoms such as hallucinations, delusions or abnormal behaviour/thought, and sedative and tranquilising effects in very disturbed or aggressive patients.
Antipsychotic drugs have a wide range of potentially serious adverse effects that may be irreversible. For this reason avoid use for non-psychotic illnesses (e.g. in anxiety or for sedation). If used for nonpsychotic illnesses, use the lowest possible dose for the shortest time.

Antipsychotic actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in various parts of the brain (in particular the limbic system). Current evidence suggests:

- All effective antipsychotics block D₂ receptors
- Differential blockade of other dopamine receptors (e.g. D₁) may influence therapeutic and adverse effects
- Antagonism of other receptors may influence antipsychotic activity, e.g. 5HT₂ antagonism with some agents.

Classification
CONVENTIONAL ANTIPSYCHOTICS
The older agents have also been classified according to their chemical structure:
- Phenothiazines (e.g. chlorpromazine)
- Butyrophenones (e.g. haloperidol)
- Diphenylbutylpiperidines (pimozide)
- Thioxanthines (e.g. flupenthixol).

In clinical practice, the terms high potency and low potency are used, see Comparative information in Conventional antipsychotics.

ATYPICAL ANTIPSYCHOTICS
The newer agents (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone) are termed atypical antipsychotics. They cannot easily be grouped by shared actions or adverse effects.

Specific considerations
Elderly: Use a lower starting dose and more gradual dose increases because of greater risk for adverse effects, including orthostatic hypotension, confusion, anticholinergic effects, acute EPSE and tardive dyskinesia. There is evidence that use of antipsychotics in older people is associated with an increased risk of stroke and sudden cardiac death.

Children: Evidence for efficacy and safety in severe behavioural disturbance is minimal. An experienced specialist should supervise antipsychotic use in behavioural disturbance or Tourette's syndrome in children.

Limit use to very disturbed children who have not responded to other medication or interventions; use with non-drug treatment; reassess frequently and limit duration of treatment.

Children and adolescents are at greater risk for acute dystonic reactions than older patients.

Pregnancy: Little information is available for atypical antipsychotics, and the conventional agents are generally preferred.

Breastfeeding: Avoid if possible, or contact one of the specialized centres, monitor infant for toxicity.

Adverse effects
Adverse effects associated with older agents appear to be less common or less severe with some of the newer antipsychotics. Overall tolerability may not be markedly different from older agents used in conservative doses.

Extrapyramidal side effects
Incidence is:
- highest with haloperidol, fluphenazine, trifluoperazine and pimozide.
- lower with chlorpromazine, pericyazine and thioridazine.
- least likely to occur with some of the atypical agents (on present information).

Reduce antipsychotic dose to avoid recurrent EPSE when possible.

Anticholinergic drugs (e.g. benztropine):
- Should not be used as routine prophylaxis for EPSE, as not all patients will be affected.
• Should be on hand for patients and their carers (who should know how and when to use them)
• May add to the intrinsic anticholinergic effects of some antipsychotics and worsen tardive dyskinesia
• Are occasionally misused for their dysphoric effects.

Dystonias: Torticollis, carpopedal spasm, trismus, perioral spasm and oculogyric crisis, as well as medical emergencies, such as laryngeal spasm and opisthotonos, may occur. Dystonias are more common in children and young adults, and more likely with high doses. They often occur within 24–48 hours of starting treatment or increasing dose, and respond rapidly to anticholinergics such as benztropine. In some cases treatment with a benzodiazepine may also prove helpful. It may be possible to reintroduce the drug at a lower dose; alternatively, consider another drug, possibly an atypical agent.

Akathisia: A feeling of motor restlessness; usually occurs 2–3 days (up to several weeks) after starting treatment and may subside spontaneously. Atypical antipsychotics may be less likely to cause akathisia. It is important to differentiate between akathisia and agitation secondary to psychosis. Akathisia tends to improve with dose reduction and deteriorate when the dose is increased; agitation due to psychosis tends to improve if the dose is increased and deteriorate if it is reduced.

Parkinsonism: Characterised by features such as tremor, rigidity or bradykinesia; usually develops after weeks or months. Although usually reversible, symptomatic treatment is sometimes necessary. Short term use of an anticholinergic (benztropine or benhexol) may be helpful. If parkinsonism persists, consider reducing antipsychotic dose or switching to an alternative antipsychotic (possibly an atypical agent).

Tardive dyskinesia (TD): Characterised by involuntary movements of the face, mouth or tongue, and sometimes head and neck, trunk or limbs. TD may appear after medium to long term treatment, or even after stopping the antipsychotic (particularly after suddenly stopping). Elderly people, smokers, diabetics and those with affective disorders appear to be at increased risk. Up to a third of people treated for 10 years with conventional antipsychotics will develop TD. There may be a slow improvement after the drug is withdrawn, particularly in young patients or early in the syndrome. The incidence of TD appears to be lower with atypical antipsychotics, particularly clozapine, although initial data need to be replicated in longer term studies.

Neuroleptic malignant syndrome (NMS)
All antipsychotics can cause NMS, a potentially fatal condition characterised by fever, marked muscle rigidity, altered consciousness and autonomic instability. The syndrome usually progresses rapidly over 24–72 hours. Elevation of serum creatine kinase concentration (skeletal muscle origin) and leucocytosis often occur. Not all typical signs need to be present for diagnosis. The incidence of NMS is greatest in young men. It does not always occur immediately after starting antipsychotic treatment, and may be seen after many months or years. Treatment involves general supportive care such as cooling, volume replacement and treatment of hyperkalaemia. Paralysis and mechanical ventilation may also be required. Anticholinergics or benzodiazepines may be helpful for muscular rigidity, and oral bromocriptine or IV dantrolene have also been used.
Other adverse effects: Chlorpromazine, in particular, is associated with a variety of skin reactions due to light exposure, including photosensitivity, phototoxicity and hyperpigmentation. Other antipsychotics may rarely cause similar skin reactions.

Comparative information
See also Table 04-1 Comparative characteristics of antipsychotic drugs.
Currently available antipsychotic drugs cannot easily be categorised according to their clinical profile and adverse effects. Choice of agent may be influenced by available formulations as well as clinical considerations. A large comparative study suggests that patients stop taking both conventional and atypical drugs at similar (high) rates over time.

Conventional antipsychotics: All conventional antipsychotics are thought to be equally effective when taken at an appropriate dose. Used in the management of schizophrenia, conventional antipsychotics reliably improve positive symptoms (e.g. hallucinations, delusions, thought disorder) and reduce relapse rates after an acute episode. Thoridizine and droperidol are more likely to cause cardiac toxicity, and should not be used routinely.

Atypical antipsychotics: The atypical agents effectively treat psychotic symptoms, have a lower incidence of EPSE than the conventional agents and may also decrease relapse rates. Some evidence suggests that clozapine may be superior to conventional agents, particularly in the management of negative symptoms (e.g. blunted affect, decreased speech, lack of motivation), or in treatment-resistant patients. This may be due to fewer EPSE and/or better patient adherence.

Incidence of serious adverse effects, such as tardive dyskinesia and neuroleptic malignant syndrome, is also probably lower than with conventional agents. Metabolic effects (e.g. weight gain, diabetes) however, are more common.
**Patient counseling**

Reinforce compliance:
- Stopping treatment or erratic compliance is associated with high risk of relapse and suicide
- Counsel patients to take medication regularly to prevent an episode, rather than after symptoms occur
- Discuss possible use of depot formulations if compliance is doubtful.

Counsel patients to avoid using illicit substances:
- Even intermittent use of cannabis or amphetamine markedly decreases control of psychotic symptoms
- Regular misuse of illicit drugs is associated with increased risk of relapse.

Explain:
- Extrapyramidal side effects, which may be alarming, and offer reassurance
- The risk of tardive dyskinesia with long term antipsychotic therapy.

Antipsychotics may impair ability to drive or operate machinery; alcohol, benzodiazepines or cannabis markedly potentiate this effect.

**Practice points**

- Never start antipsychotic therapy using a depot formulation, as appropriate dose titration is impossible and any acute adverse effect will be persistent
- Use the lowest effective dose, especially if continuous treatment is required
- Monitor carefully for clinical improvement; consider possible reasons for non-response (e.g. poor compliance, substance misuse, drug interactions, inadequate dose)
- Agitated patients respond better to drugs that are more sedating; withdrawn patients respond better to the less sedating or atypical agents
- Avoid use of >1 antipsychotic, except in periods of ‘cross-over’ from one drug to another, and when needed to augment depot treatment (when a dose increase can take 3–6 months to take effect)
- Adding a benzodiazepine may allow antipsychotic dose reduction in acute psychotic states exhibiting acute agitation
- Individualise duration of treatment; prophylactic treatment is usually continued for 1–2 years after remission of a first psychotic episode, in order to prevent relapse (which may occur several weeks after stopping treatment); and for longer after >2 episodes
- After an initial period of stabilisation, the long half-life of most antipsychotics allows the total daily oral dose to be given at night in most patients
- Withdraw antipsychotics slowly to avoid rapid relapse and withdrawal symptoms (tachycardia, sweating, insomnia) with those drugs that have prominent anticholinergic effects; benztprine may be used for several weeks in such an event
- All patients need baseline and regular monitoring of weight, blood glucose, BP and lipids
- Routine full blood counts and liver function tests are advisable, particularly during the first months of treatment, and are mandatory with clozapine.

### 04.02.01 Conventional antipsychotics

**CHLORPROMAZINE, FLUPHENAZINE, HALOPERIDOL, TRIFLUOPERAZINE, ZUCLOPENTHIXOL**

**Mode of action**

Antagonise dopamine D2 receptors, resulting in antipsychotic effects.

**Indications**

- Treatment of acute and chronic psychoses (eg schizophrenia)
- Acute mania
- Organic psychoses (eg dementia-associated agitation)
- Severe behavioural disorders in children
- Adjunct in psychotic depression
- Adjunct in anaesthesia
- Adjunct in treatment of alcoholic hallucinosis
- Tourette’s syndrome and other choreas
- Intractable nausea and vomiting (haloperidol)
- Intractable hiccup (chlorpromazine)

**Contraindications**

- Previous allergic reaction, Profound CNS depression or coma (including those resulting from alcohol or other drugs), Phaeochromocytoma.
**Specific considerations**

**Parkinson's disease:** risk of aggravation; potential for drug interactions with usual treatments; clozapine is generally preferred.

**Respiratory failure:** phenothiazines may cause respiratory depression or worsen that associated with alcohol, benzodiazepines or barbiturates.

**Epilepsy:** may lower seizure threshold.

**Hyperthyroidism:** increased risk of acute dystonia.

**Cardiovascular disease:** may increase QT interval; increased risk of arrhythmia.

**Closed angle glaucoma,** increased intraocular pressure, GI obstruction, prostatism, urinary retention, myasthenia gravis: may be exacerbated by the anticholinergic effects of antipsychotics.

**Previous blood dyscrasias:** may increase risk of recurrence.

**Hepatic impairment:** Use with caution; halve dose in severe impairment. Avoid chlorpromazine.

**Surgery:** Reduced doses of anaesthetics and CNS depressants may be necessary; additive hypotension may occur.

**Elderly:** Use a lower starting dose and more gradual dose increases because of greater risk for adverse effects, including orthostatic hypotension, confusion, anticholinergic effects, acute extrapyramidal side effects (EPSE) and tardive dyskinesia.

**Children:** Conventional antipsychotics, in particular haloperidol, have been associated with tardive and withdrawal dyskinesias in children which may not be reversible. Children may not complain of the sensation of akathisia in the same way as adults; monitor closely. Thioridazine is contraindicated in children due to risk of cardiotoxicity. More sedating agents such as chlorpromazine are more likely to impair cognition and therefore learning at school. Evidence for efficacy and safety in severe behavioural disturbance is poor. An experienced specialist should supervise antipsychotic use in behavioural disturbance or Tourette's syndrome in children.

**Pregnancy:** All ADEC category C, except pimozide and thiothixene, which are ADEC category B1. Avoid if possible, or use the lowest effective dose, although poorly controlled psychotic disorders may compromise maternal health and pregnancy outcome. Neonatal adverse effects observed include generalised hypertonicity and dystonic reactions. Consider supervised dose reduction or stop temporarily for 7–10 days before delivery.

**Breastfeeding:** Avoid use when possible, or seek specialist advice If used, monitor infant for toxicity.

**Adverse effects**

**Common:** sedation, orthostatic hypotension, tachycardia, dry mouth, blurred vision, mydriasis, constipation, nausea, urinary retention, sexual adverse effects, EPSE, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility).

**Infrequent:** allergic reactions, including urticaria, erythema multiforme, photosensitivity (chlorpromazine); pigmentary changes of skin or eyes (particularly thioridazine), corneal and lens opacities, hyperthermia, hypothermia, SIADH.

**Rare:** anaemia, thrombocytopenia, agranulocytosis, neuroleptic malignant syndrome, retinitis pigmentosa (particularly thioridazine), ECG changes (reversible, broadened QT interval), arrhythmias, cardiac arrest, sudden death, hepatic fibrosis, cholestatic jaundice (chlorpromazine), systemic lupus erythematosus, convulsions, hyperglycaemia (chlorpromazine, haloperidol).

**Patient counselling**

This medicine may cause drowsiness and may increase the effects of alcohol. Do not drive or operate machinery if you are affected.

You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.

**Practice points**

- avoid using conventional antipsychotics routinely for short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders outside the hospital setting; even though many antipsychotics have marketing approval for this purpose, benzodiazepines may be more appropriate

**CHLORPROMAZINE**

**Mode of action**

Antagonise dopamine D₂ receptors, resulting in antipsychotic effects.

**Indications**

Treatment of acute and chronic psychoses
Short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders
Severe behavioural disorders in children
Intractable hiccup, if non-drug treatment fails

**Contraindications**
Previous allergic reaction
Profound CNS depression or coma (including those resulting from alcohol or other drugs)
Phaeochromocytoma
Specific considerations
Hepatic impairment
Avoid use in moderate-to-severe impairment.

**Specific considerations**
Parkinson's disease: risk of aggravation; potential for drug interactions with usual treatments; clozapine is generally preferred. See Comparative information in Atypical antipsychotics.
Respiratory failure: phenothiazines may cause respiratory depression or worsen that associated with alcohol, benzodiazepines or barbiturates.
Epilepsy: may lower seizure threshold.
Hyperthyroidism: increased risk of acute dystonia.
Cardiovascular disease: may increase QT interval; increased risk of arrhythmia.
Closed angle glaucoma, increased intraocular pressure, GI obstruction, prostatism, urinary retention, myasthenia gravis: may be exacerbated by the anticholinergic effects of antipsychotics.
Previous blood dyscrasias: may increase risk of recurrence.
Hepatic impairment: Use with caution; halve dose in severe impairment. Avoid chlorpromazine.
Surgery: Reduced doses of anaesthetics and CNS depressants may be necessary; additive hypotension may occur.
Elderly: Use a lower starting dose and more gradual dose increases because of greater risk for adverse effects, including orthostatic hypotension, confusion, anticholinergic effects, acute EPSE and tardive dyskinesia.
Children: Conventional antipsychotics, in particular haloperidol, have been associated with tardive and withdrawal dyskinesias in children which may not be reversible. Children may not complain of the sensation of akathisia in the same way as adults; monitor closely. Thioridazine is contraindicated in children due to risk of cardiotoxicity. More sedating agents such as chlorpromazine are more likely to impair cognition and therefore learning at school.
Evidence for efficacy and safety in severe behavioural disturbance is poor. An experienced specialist should supervise antipsychotic use in behavioural disturbance or Tourette's syndrome in children.
Limit use to very disturbed children who have not responded to other medication or interventions; use with non-drug treatment; reassess frequently and limit duration of treatment.
Children and adolescents are at greater risk for acute dystonic reactions than older patients.

**Pregnancy:** All ADEC category C, except pimozide and thiothixene, which are ADEC category B1. Avoid if possible, or use the lowest effective dose, although poorly controlled psychotic disorders may compromise maternal health and pregnancy outcome. Neonatal adverse effects observed include generalised hypertonicity and dystonic reactions. Consider supervised dose reduction or stop temporarily for 7–10 days before delivery.
**Breastfeeding:** Avoid use when possible, or contact one of the

**Adverse effects**
Common: sedation, orthostatic hypotension, tachycardia, dry mouth, blurred vision, mydriasis, constipation, nausea, urinary retention, sexual adverse effects, EPSE, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility)
Infrequent: allergic reactions, including urticaria, erythema multiforme, photosensitivity (chlorpromazine); pigmentedary changes of skin or eyes (particularly thioridazine), corneal and lens opacities, SIADH, hyperthermia, hypothermia
Rare: anaemia, thrombocytopenia, agranulocytosis, neuroleptic malignant syndrome, retinitis pigmentosa (particularly thioridazine), ECG changes (reversible, broadened QT interval), arrhythmias, cardiac arrest, sudden death, hepatic fibrosis, cholestatic jaundice (chlorpromazine), systemic lupus erythematosus, seizures, increased blood glucose (particularly chlorpromazine, haloperidol)

**Dosage**
Chronic psychoses: Oral, 25–100 mg 3–4 times daily. Maximum, 1000 mg daily.
Acute psychoses
Oral, 50–100 mg up to every 2 hours as needed, up to 500 mg daily.
IV/IM, 25–50 mg up to 3–4 times daily.
Agitation, anxiety, disturbed behaviour
IM, 25 mg initially, in acute cases. If needed, a second dose may be given after at least an hour.
Oral, 25–50 mg up to 3 times daily.
Behaviour disorder, child >5 years
Oral, 0.5–1 mg/kg every 4–6 hours.
IV, 0.25–1 mg/kg every 6–8 hours.
Maximum (all routes), 75 mg daily.

**Patient counselling**
Avoid excessive skin exposure to sunlight and sunlamps while taking this medicine; wear protective clothing and use sunscreen.
This medicine may cause drowsiness and may increase the effects of alcohol. Do not drive or operate machinery if you are affected.
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.

**Practice points**
- less likely than many antipsychotics to cause extrapyramidal reactions, especially if daily dose is <600 mg, but there is considerable variation between patients
- use in children requires specialist psychiatric supervision
- because it can cause phototoxic skin reactions, chlorpromazine is a poor choice for children and those who work outdoors
- be cautious using chlorpromazine for intractable hiccup or nausea and vomiting, even though both are marketed indications, as risk of adverse effects may outweigh benefits
- avoid using conventional antipsychotics routinely for short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders outside the hospital setting; even though many antipsychotics have marketing approval for this purpose, benzodiazepines may be more appropriate

**Products**
CHLORPROMAZINE TABS 100 MG (AS HCL) (NEURAZINE®)

**FLUPHENAZINE**

**Mode of action**
Same as Chlorpromazine

**Indications**
Treatment of chronic psychoses (injection)
Treatment of acute and chronic psychoses (oral liquid)
Acute mania
Organic psychoses (eg dementia-associated agitation)
Severe behavioural disorders in children
Adjunct in psychotic depression
Adjunct in anaesthesia
Adjunct in treatment of alcoholic hallucinosis
Tourette’s syndrome and other choreas

**Contraindications**
Same as Chlorpromazine

**Specific considerations**
Same as Chlorpromazine

**Adverse effects**
Same as Chlorpromazine

**Dosage**
IM, 12.5–50 mg every 2–6 weeks. Maximum, 100 mg IM every 2 weeks.
Oral, 2.5–10 mg daily in 2 or 3 divided doses.

**Patient counselling**
Same as Chlorpromazine

**Practice points**
- onset of action for injection is 1–3 days
- use 100 mg/mL injection strength if volumes >2–3 mL are required
- give a 12.5 mg test dose to patients not previously treated with depot antipsychotics to check for adverse effects (use a lower dose for frail or elderly patients)
• avoid using conventional antipsychotics routinely for short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders outside the hospital setting; even though many antipsychotics have marketing approval for this purpose, benzodiazepines may be more appropriate

**Products**

FLUPHENAZINE AMPS 25 MG / AMP (AS DECONATE) 1 ML AMP (MODECATE®)

**HALOPERIDOL**

**Mode of action**
Same as Chlorpromazine

**Indications**
Marketed
Treatment of acute and chronic psychoses
Treatment of acute mania
Tourette's syndrome and other choreas
Adjunct in treatment of alcoholic hallucinosis
Intractable nausea and vomiting (see Haloperidol (Gastrointestinal drugs))
Accepted: Intractable hiccups, Short term management of acute, severe anxiety, agitation or disturbed behaviour in non-psychotic disorders

**Contraindications**
Same as Chlorpromazine

**Specific considerations**
Risk factors for prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.

**Adverse effects**
Same as Chlorpromazine

**Dosage**
Chronic psychoses
Oral, 1–5 mg 2–3 times daily. Maximum 30 mg daily.
Depot IM, 50–300 mg every 4 weeks.
Acute psychoses and mania
Oral, 5–10 mg every 2 hours as needed.
Short acting IM, 2–10 mg every hour as needed.
Agitation, anxiety, disturbed behaviour
Oral, 1–5 mg 2–3 times daily.
Short acting IM/IV, 2–10 mg single dose, repeat every 2–6 hours if needed; maximum 15 mg in 24 hours.
Elderly: Use low doses (0.5–10 mg daily) to avoid severe extrapyramidal reactions.
Child > 5 years
Chronic psychoses, oral, initially 0.25–0.5 mg once daily, increased to 0.15 mg/kg daily (maximum 5 mg).
Tourette's syndrome, oral, initially 0.25–0.5 mg once daily, increased to 0.05 mg/kg daily (maximum 5 mg).
May be given in 2 or 3 divided doses.

**Dose equivalence**
Initial dose of haloperidol depot injection is 10–15 times the previous oral daily dose of haloperidol every 4 weeks; maximum 100 mg.

**Patient counselling**
Same as Chlorpromazine

**Practice points**
• use with a benzodiazepine to increase sedation for acutely psychotic patients
• often used for the elderly because of the low incidence of hypotension and anticholinergic effects, but has a relatively high incidence of EPS
• evidence for efficacy in hiccups is poor; balance risk of adverse effects against likely benefit
• avoid using conventional antipsychotics routinely for short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders outside the hospital setting; even though many antipsychotics have marketing approval for this purpose, benzodiazepines may be more appropriate

**Depot injection**
• divide injection volumes > 3 mL in half and give at 2 sites
onset of action is 2–4 days
it is occasionally necessary to give doses every 2–3 weeks; sometimes a longer dosage interval is needed (up to every 6 weeks)

Products
HALOPERIDOL AMPS 5 MG/AMP 1 ML AMP (HALOPERIDOL®)
HALOPERIDOL AMPS 100 MG/AMP 1 ML AMP (HALDOL DECANOAS®)
HALOPERIDOL ORAL DROPS 2 MG/ML 15 ML BOTTLE (HALDOL®)
HALOPERIDOL TABS 5 MG (HALDOL®, SERENACE®)

TRIFLUOPERAZINE

Mode of action
Same as Chlorpromazine

Indications
Treatment of acute and chronic psychoses
Short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders
Acute mania, Adjunct in psychotic depression
Adjunct in anaesthesia
Adjunct in treatment of alcoholic hallucinosis
Tourette's syndrome and other choreas

Contraindications
Same as Chlorpromazine

Specific Considerations
Same as Chlorpromazine

Adverse effects
Same as Chlorpromazine

Dosage
Adult: 2–15 mg twice daily, to a maximum of 50 mg daily.
Child >6 years: 0.025–0.1 mg/kg twice daily. Maximum, 4 mg daily.

Patient counselling
Same as Chlorpromazine

Practice points

• avoid using conventional antipsychotics routinely for short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders outside the hospital setting; even though many antipsychotics have marketing approval for this purpose, benzodiazepines may be more appropriate

Products
TRIFLUOPERAZINE TABS 5 MG (AS HCL) (STELAZINE®)

ZUCLOPENITHIXOL

Mode of action
Same as Chlorpromazine

Indications
Initial treatment of acute psychoses
Treatment of chronic psychoses
Acute mania
Organic psychoses (eg dementia-associated agitation)
Severe behavioural disorders in children
Adjunct in psychotic depression
Adjunct in anaesthesia
Adjunct in treatment of alcoholic hallucinosis
Tourette's syndrome and other choreas

Contraindications
Same as Chlorpromazine

Specific considerations
Same as Chlorpromazine

Adverse effects
Same as Chlorpromazine
Dosage
Acute psychoses, acute mania
Oral, 10–50 mg daily. Doses of up to 75 mg daily may be needed in severe cases.
Intermediate acting IM, 50–150 mg every 2–3 days, up to 400 mg per course (up to 4 doses); treat for a maximum of 2 weeks before switching to alternative zuclopenthixol formulation.
Chronic psychoses: Depot IM, 200–400 mg every 2–4 weeks. Oral, 20–40 mg daily.

Dose equivalence
The manufacturer suggests an oral dose of 25 mg daily is equivalent to a 200 mg depot injection every 2 weeks or 400 mg every 4 weeks.
An oral dose of 40 mg daily is considered to be equivalent to an intermediate acting injection dose of 100 mg every 2–3 days.

Patient counselling
Same as Chlorpromazine

Practice points
- maintenance treatment with an oral or depot preparation is usually begun after 1 or 2 injections of intermediate acting zuclopenthixol injection
- if changing from intermediate acting zuclopenthixol injection to a depot preparation, give the first depot dose with the last injection
- if changing from intermediate acting zuclopenthixol injection to oral therapy, give the first oral dose 2–3 days after the last injection
- avoid using conventional antipsychotics routinely for short term management of anxiety, agitation or disturbed behaviour in non-psychotic disorders outside the hospital setting; even though many antipsychotics have marketing approval for this purpose, benzodiazepines may be more appropriate

Intermediate acting injection
- may be useful in highly disturbed patients who are poorly compliant with oral drugs; not recommended in acute psychosis due to organic disorders
- sedation is significant in the first few hours after the first injection, maximal at 12 hours, and may last up to 3 days

Products
ZUCLOPENTHIXOL ACUPHASE AMPS 100 MG/AMP (AS ACETATE) 2 ML AMP (CLOPIXOL®)
ZUCLOPENTHIXOL AMPS 200 MG/AMP (AS DECONATE) 1 ML AMP (CLOPIXOL®)

04.02.02 Atypical antipsychotic drugs

AMISULPRIDE

Mode of action
D₂/D₃ antagonist predominantly in the limbic area. Low affinity for serotonin, alpha-adrenergic, histaminic and muscarinic receptors.
Individual agents act as antagonists at different dopamine receptor subtypes. All except amisulpride act as 5HT₂ receptor antagonists.

Indications
Schizophrenia, Treatment of acute and chronic psychoses.
Organic psychoses, e.g. dementia-associated agitation.

Specific considerations
Prolonged QT interval or risk factors for prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
Parkinson's disease: risk of aggravation; clozapine is generally preferred.
Seizures: atypical antipsychotics lower seizure threshold; use with caution.
Renal impairment: Reduce dose in mild-to-moderate impairment. No data in severe impairment; avoid use.
Elderly: Use a lower starting dose and more gradual dose increases because of greater risk for adverse effects, including orthostatic hypotension, confusion, acute EPSE and tardive dyskinesia. See also Adverse effects.
Pregnancy: ADEC category B3.

Adverse effects
Common: dose-related EPSE (including acute dystonia and tardive dyskinesia), insomnia, anxiety, agitation, somnolence, amenorrhea, galactorrhoea, hypersalivation, constipation.
Infrequent: orthostatic hypotension.
Rare: seizures, bradycardia, QT prolongation, neuroleptic malignant syndrome.
Hyperglycaemia, EPSE, dystonia, akathisia, parkinsonism, tardive dyskinesias and neuroleptic malignant syndrome
have been reported with most atypical agents (clozapine and olanzapine in particular).

**Dosage**
- Acute psychosis, 400–800 mg daily in 2 divided doses.
- Maintenance, predominantly negative symptoms, 50–300 mg once daily.
- Maintenance, mixed positive and negative symptoms, adjust dose to minimum required to control positive symptoms.
- Renal impairment: Halve the dose in mild impairment; give one-third dose in moderate impairment.

**Patient counseling**
This medicine may cause drowsiness and may increase the effects of alcohol. Do not drive or operate machinery if you are affected.
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.

**Practice points**
- Data comparing amisulpride with haloperidol show a trend towards increased efficacy with amisulpride for negative symptoms
- Although the maximum recommended dose is 1200 mg, doses >800 mg daily result in increased adverse effects without evidence of increased benefit
- Supply of atypical antipsychotics is subsidised through the PBS only when used to treat schizophrenia and related conditions
- Clinical effectiveness of olanzapine, quetiapine and risperidone as monotherapy for mania is not established, see Bipolar disorder.

**Products**
AMISULPRIDE TABS 200 MG (SOLIAN®)

**CLOZAPINE**

**Mode of action**
It act as 5HT2 receptor antagonist.

**Indications**
Schizophrenia in people unresponsive to, or intolerant of, other antipsychotics (i.e. lack of satisfactory clinical response, despite the use of adequate doses of drugs from at least 2 groups of antipsychotics for a reasonable duration; or development of extrapyramidal reactions, including tardive dyskinesia).

**Contraindications**
Drug-induced (including clozapine-induced) neutropenia or agranulocytosis, Bone marrow disorders, Circulatory collapse, CNS depression from any cause, Alcoholic or toxic psychosis, Poorly controlled epilepsy, Severe cardiac, hepatic or renal disease, Paralytic ileus.

**Specific considerations**
History of seizures: clozapine lowers seizure threshold, causing EEG changes, myoclonic jerks or generalised seizures.
Prostatism, GI obstruction, closed angle glaucoma: may be exacerbated by anticholinergic activity of clozapine.
Drugs which may cause agranulocytosis: additive risk of agranulocytosis; avoid combinations.
Children: Efficacy and safety are not established; neutropenia seems to be more common in children and adolescents than adults.
Pregnancy: ADEC category C.
Breastfeeding: Contact specialised information service).

**Adverse effects**
Common: drowsiness (occurs in 40%), seizures, headache, dizziness, orthostatic hypotension (especially at start of treatment), tachycardia, hyperpyrexia (5%), hepatitis, neutropenia, hypersalivation (can cause aspiration pneumonia), weight gain, nausea, vomiting, constipation, urinary retention, urinary incontinence.
Infrequent: agranulocytosis, eosinophilia, priapism, EPSE.
Rare: cardiomyopathy, myocarditis, ECG changes, arrhythmias, hypertension, gynaecomastia, galactorrhoea, hyperglycaemia, myoclonic jerks, neuroleptic malignant syndrome, interstitial nephritis, respiratory arrest.

**Dosage**
12.5 mg, increased to 25–50 mg on second day. If well tolerated, increase in 25–50 mg increments to 300 mg daily within 2–3 weeks. Then increase in 50–100 mg increments at 4–7-day intervals if required. Give single daily doses
of <300 mg in the evening.
Usual range: 200–600 mg daily.
Maximum: 900 mg daily.

**Patient counseling**
You will need to have regular blood tests and other checks while taking clozapine to help your doctor look out for serious side effects.
Do not stop taking this medicine suddenly unless your doctor tells you to.
Tell your doctor if you start to smoke, or if you stop smoking, because your clozapine dose may need to be changed.
This medicine may cause drowsiness and may increase the effects of alcohol. Do not drive or operate machinery if you are affected.
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.

**Practice points**
- National distribution system for clozapine requires registration of medical practitioners, pharmacists and patients
- Start treatment only if white cell count and absolute neutrophil count are normal; blood monitoring is required each week for the first 18 weeks and then each month; see manufacturer's product information for further details
- Medical supervision and resuscitation facilities must be available when treatment starts, because of possible profound orthostatic hypotension with respiratory or cardiac failure
- When switching from another antipsychotic, avoid overlapping therapy unless there is close supervision and observation; otherwise, reduce the antipsychotic over 1 week and stop for 24 hours before starting clozapine
- After stopping depot antipsychotics, start clozapine 1 week after scheduled time of next injection
- If seizures occur, reduce dose; consider using valproate (not carbamazepine)
- If treatment is reinstituted after an interval of >2 days, restart at 12.5 mg daily
- Where possible do not stop abruptly; withdraw over 1–2 weeks (observe mental state and for cholinergic rebound symptoms), but do not delay stopping if a serious adverse effect occurs
- Serum clozapine concentrations may help to determine the appropriate dose.

**Products**
- CLOZAPINE TABS 25 MG (LEPONEX®)
- CLOZAPINE TABS 100 MG (CLOZAPINE®, LEPONEX®)

**OLANZAPINE**

**Mode of action**
It acts as 5HT₂ receptor antagonist.

**Indications**
Schizophrenia and related psychoses, Acute mania, Behavioural and psychological symptoms in dementia (IM only), Maintenance treatment in bipolar disorder.

**Specific considerations**
- Prostatic enlargement, paralytic ileus, closed angle glaucoma: may worsen (has anticholinergic effects).
- Parkinson's disease: risk of aggravation; clozapine is generally preferred.
- Children: Efficacy and safety not established in those <18 years.
- Pregnancy: Contact specialised information service ADEC category B3.
- Breastfeeding: Contact specialised information service.

**Adverse effects**
Common: hyperglycaemia (random blood glucose at upper limit of normal), type 2 diabetes, weight gain, dizziness, peripheral oedema, orthostatic hypotension, dry mouth, constipation, drowsiness.
Infrequent: agitation, EPSE, elevation of liver transaminases.
Rare: neutropenia, galactorrhoea, gynaecomastia, VTE, amenorrhoea, , neuroleptic malignant syndrome, rhabdomyolysis, hypercholesterolaemia, hypertriglyceridaemia.

**Dosage**
**Adult**
Schizophrenia and related psychoses, oral, start at 10 mg daily, increase daily dose by 2.5–5 mg as clinically indicated, to 20 mg daily or more.
Agitation in schizophrenia or acute mania, IM 5–10 mg, followed if necessary by further doses of up to 10 mg at 2 and 6 hours after initial dose; maximum 30 mg in 24 hours.
Behavioural and psychological symptoms in dementia, IM, 2.5 mg, followed if necessary by up to 5 mg at 2 and 6 hours after initial dose. Maximum 12.5 mg in 24 hours.

Acute mania and maintenance treatment in bipolar disorder, oral 5–20 mg daily.

Elderly, renal or hepatic impairment: Oral, start with 5 mg daily.

**Patient counseling**

This medicine may cause drowsiness and may increase the effects of alcohol. Do not drive or operate machinery if you are affected.

You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy. Tell your doctor if you start to smoke, or if you stop smoking, as your dose may need to be changed.

**Practice points**

- Response to tablets may occur in 1–2 weeks; allow 2–3 months for full trial
- It is possible to overlap drugs when switching from another antipsychotic provided there is close supervision and monitoring
- After stopping depot antipsychotics, start oral olanzapine at scheduled time of next injection
- Experts suggest that doses >20 mg daily (the current maximum suggested in manufacturer's information) may be required in some patients with schizophrenia
- Check glucose tolerance if patient gains weight
- Use wafer formulation for acutely psychotic patients, those who have difficulty swallowing tablets, or to help ensure compliance
- Monitor for cardiovascular effects, such as hypotension, for 2 hours after each IM injection.
- Supply of atypical antipsychotics is subsidised through the PBS only when used to treat schizophrenia and related conditions
- Clinical effectiveness of olanzapine, quetiapine and risperidone as monotherapy for mania is not established, see Bipolar disorder

**Products**

OLANZAPINE TABS 5 MG (PREXAL®, ZYPREXA®)

**QUETIAPINE**

**Mode of action**

It acts as 5HT2 receptor antagonist.

**Indications**

Schizophrenia, Acute mania.

**Specific considerations**

- Prolonged QT interval or risk factors for prolonging the QT interval, see Prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
- Seizures: atypical antipsychotics lower seizure threshold; use with caution.
- Parkinson's disease: risk of aggravation; clozapine is generally preferred.
- Hepatic impairment: Use a conservative dose in severe impairment.
- Elderly: Use a lower starting dose and more gradual dose increases because of greater risk for adverse effects, including orthostatic hypotension, confusion, acute extrapyramidal side effects (EPSE) and tardive dyskinesia
- Children: Efficacy and safety not established in people <18 years.
- Pregnancy: ADEC category B3.
- Breastfeeding: Contact specialised information service.

**Adverse effects**

- Common: drowsiness, dizziness, orthostatic hypotension, tachycardia, dry mouth, constipation.
- Infrequent: elevation of liver transaminases, weight gain.
- Rare: leucopenia, neuroleptic malignant syndrome, dyslipidaemias.

**Dosage**

Schizophrenia: 25 mg twice daily, increasing gradually as tolerated over 3 or more days to 150 mg twice daily. Further adjustment up to a total daily dose of 750 mg or more may be required depending upon response.

Acute mania: 50 mg twice daily, increasing gradually as tolerated over 3 days to 200 mg twice daily. Further adjustment up to a total daily dose of 800 mg may be required.

**Patient counselling**

This medicine may cause drowsiness and may increase the effects of alcohol. Do not drive or operate machinery if
you are affected. You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.

Practice points
- Twice daily dosing is needed; quetiapine has a relatively short half-life
- Usually causes only transient elevations of serum prolactin
- Sedative effect may be therapeutic in acute psychoses
- Preliminary data suggest incidence of EPSE may be lower than with other atypical agents apart from clozapine.

Products
QUETIAPINE TABS 25 MG (SEROQUEL®)
QUETIAPINE TABS 200 MG (SEROQUEL®)

RISPERIDONE

Mode of action
It acts as 5HT2 receptor antagonist.

Indications
Schizophrenia and related psychoses, Behaviour disturbance in dementia, Conduct and other disruptive disorders in adults and children >5 years with subaverage intellectual functioning or mental retardation, Short term treatment of acute mania, Behavioural disorders in children and adolescents with autism.

Specific consideration
Parkinson's disease: risk of aggravation; clozapine is generally preferred.
Renal impairment: Dose reduction may be required.
Hepatic impairment: The manufacturer suggests using half the usual starting and incremental doses in people with established hepatic impairment.
Elderly: Use half the usual starting and incremental doses. In clinical trials elderly people with dementia-related psychosis treated with risperidone had a higher incidence of cerebrovascular adverse events compared to people taking placebo. See adverse effects.
Children: Efficacy and safety are not established other than in conduct and other disruptive disorders, and short term use in moderate-to-severe behaviour disturbance associated with autism.
Pregnancy: ADEC category B3.
Breastfeeding: Contact specialised information service.

Adverse effects
Common: orthostatic hypotension (especially early in treatment), tachycardia, insomnia, agitation, anxiety, headache, akathisia, hyperprolactinaemia.
Infrequent: rhinitis, weight gain, nausea, constipation, blurred vision, incontinence, sexual adverse effects, gynaecomastia, galactorrhoea, amenorrhoea, drowsiness, EPSE other than akathisia (but common in higher doses and in acute mania).
Rare: seizures, body temperature deregulation, tardive dyskinesia, neuroleptic malignant syndrome, water intoxication due to SIADH or polydipsia, hepatotoxicity, hyperglycaemia, exacerbation of pre-existing type 2 diabetes, TIA, stroke.

Dosage
Schizophrenia
Adult
Total daily dose can be given as a single dose or in 2 divided doses.
Oral, 1 mg twice daily, increasing by 1 mg twice daily each day. Usual range 4–6 mg daily; daily doses >4 mg increase the risk of EPSE.
Depot IM, 25 mg every 2 weeks. Give supplemental antipsychotic for the first 3 weeks. Dose may need to be increased to 37.5–50 mg every 2 weeks, but do not adjust dose more frequently than every 4 weeks. Effects of a dose increase will not be seen for 3 weeks.
Elderly, renal or hepatic impairment
Oral, 0.5 mg once or twice daily, increasing by 0.5 mg once or twice daily every second day, up to 4 mg daily.
Depot IM, 25 mg every 2 weeks may be appropriate, see manufacturer's product information.

Behaviour disturbance in dementia: Oral, 0.25 mg twice daily, increasing by 0.25 mg every 2 or more days. Usual range 0.5–1 mg twice daily.
Conduct and other disruptive behaviour disorders, age >5 years
>50 kg, oral, 0.5 mg once daily, increasing by 0.5 mg daily every other day as needed. Usual range 0.5–1.5 mg daily.
<50 kg, oral, 0.25 mg once daily, increasing by 0.25 mg daily every other day as needed. Usual range 0.25–0.75 mg daily.

Acute mania: Oral, 2 mg once daily, increasing if necessary by 1 mg daily. Usual dose range 2–6 mg daily.

**Patient counselling**
This medicine may cause drowsiness and may increase the effects of alcohol. Do not drive or operate machinery if you are affected.
You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this; sit or lie down if you become dizzy.

**Practice points**
- It is possible to overlap the drugs when switching from another antipsychotic, provided there is close supervision and monitoring
- After stopping depot antipsychotics, start oral risperidone at a low dose at the scheduled time of next injection
- Response occurs in 1–2 weeks; allow 2–3 months for full trial
- Use wafer formulation for patients who have difficulty swallowing tablets, or to help ensure compliance
- Once daily dosing with tablets may be suitable once the patient is stabilized.
- supply of atypical antipsychotics is subsidised through the PBS only when used to treat schizophrenia and related conditions
- clinical effectiveness of olanzapine, quetiapine and risperidone as monotherapy for mania is not established, see Bipolar disorder

**Products**
RISPERIDONE TABS 1 MG (RISPERDAL®, RAXIDONE®)
RISPERIDONE TABS 4 MG (RAXIDONE®, RESPAL®, RISPERDAL®)

**SULPIRIDE (LEVOSULPIRIDE)**

**Mode of action**
Selective antagonist of central dopamine (D2, D3, and D4) receptors.

**Adverse Effects, Treatment, and Precautions**
Sleep disturbances, overstimulation, agitation, mild extrapyramidal effects, tardive dyskinesia and minimal antimuscarinic effects. Cardiovascular effects such as hypotension are generally rare although they may occur with overdose.
Sulpiride should be given with care to manic or hypomanic patients in whom it may exacerbate symptoms.

**Indications**
Sulpiride is mainly used in the treatment of psychoses such as schizophrenia. It has also been given in the management of Tourette’s syndrome, anxiety disorders, vertigo, and benign peptic ulceration.

**Specific Considerations**
Porphyria: Sulpiride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals.
Gastrointestinal drugs: Giving sulpiride with therapeutic doses of sucralfate or an antacid containing aluminium and magnesium hydroxides may reduce the mean oral bioavailability of sulpiride, and it was recommended that sulpiride should be given before, rather than with or after, sucralfate or antacids.
Chorea: Antipsychotics have some action against choreiform movements as well as being of use to control the behavioural disturbances of Huntington’s chorea.
Renal Impairment: Dosage adjustment is also advised in patients with renal impairment.
Breast feeding: Sulpiride may be distributed into breast milk in relatively large amounts

**Dosage**
In the treatment of schizophrenia initial doses of 200 to 400 mg of sulpiride are given twice daily by mouth, increased if necessary up to a maximum of 1.2 g twice daily in patients with mainly positive symptoms or up to a total of 800 mg daily in patients with mainly negative symptoms.
IM usual doses range from 200 to 800 mg daily.
Children: A daily dose of 3 to 5 mg/kg may be given by mouth to children over 14 years of age.
Elderly: Lower initial doses have been recommended in elderly patients, subsequently adjusted as required.

**Products**
SULPIRIDE TABS 200 MG (DOGMATIL®, SULPIREN®)
04.02.03 Bipolar disorder drugs

**LITHIUM**

**Mode of action**
Unknown; its actions include inhibition of dopamine release, enhancement of serotonin release and decreased formation of intracellular second messengers. Lithium has little or no psychotropic effect in normal individuals.

**Indications**
Marketed: Prevention of manic or depressive episodes in bipolar disorder, Treatment of acute mania Schizoaffective disorder and chronic schizophrenia.
Accepted: Augmentation for treatment-resistant depression.

**Specific considerations**
Acute hyponatraemia (e.g. Addison's disease, dehydrated or debilitated patients, low sodium diet): increased risk of lithium toxicity.
Psoriasis: may be exacerbated or precipitated by lithium.
Treatment with drugs which can contribute to the serotonin syndrome: likelihood of serotonin syndrome may be increased; avoid combinations or monitor clinical course carefully, see Table 04-02 Drugs that may contribute to serotonin syndrome.
Renal impairment: Reduce dose even in relatively mild renal dysfunction; monitor serum lithium concentration frequently when renal function is unstable. Unacceptably high risk of lithium toxicity in severe impairment.
Surgery: Consider suspending treatment briefly during preoperative and perioperative periods, as fasting and changes in fluid intake or dynamics may alter concentration.
Elderly: In addition to age-related decline in renal function, older people are more sensitive to toxic effects; use lower doses and monitor more frequently.

**Adverse effects**
Common: metallic taste, nausea, epigastric discomfort, diarrhoea, weight gain, fatigue, headache, vertigo, tremor, acne, psoriasis, leucocytosis, polyuria, hypothyroidism, benign T wave changes on ECG.
Infrequent: nephrogenic diabetes insipidus with polydipsia and polyuria, memory impairment, hair loss, hyperparathyroidism.
Rare: cardiac arrhythmias, hyperthyroidism.
Mild-to-moderate toxicity
- blurred vision, increasing diarrhoea, nausea, vomiting, muscle weakness, drowsiness, apathy, ataxia, flu-like illness.
- Severe toxicity: increased muscle tone, hyper-reflexia, myoclonic jerks, coarse tremor, dysarthria, disorientation, psychosis, seizures, coma.
Nephrotoxicity: Renal damage has never been conclusively demonstrated for those with well-controlled lithium treatment without multiple episodes of acute toxicity.

**Dosage**
Acute mania: Initially 750–1000 mg daily in divided doses (every 12 hours if using controlled release product); increase dose by 250–500 mg daily (depending on serum concentration) until symptoms resolve. Maximum dose 2500 mg daily.
Prophylaxis: 250–1000 mg daily in divided doses (every 12 hours if using controlled release product) for 2 weeks, then adjust dose according to serum concentration.
Elderly, renal impairment: Use reduced dose and monitor carefully.

**Concentration monitoring**
Take blood for lithium concentration at least 8–12 hours after last dose.
Measure concentration 5–7 days after starting treatment and after each dose change until stabilised, then every 3 months. Steady state may not be reached for 4–7 days (longer in the elderly or those with renal impairment).
Monitor lithium concentration more frequently during illness (e.g. gastroenteritis), manic or depressive phases, changes in diet or temperature, pregnancy and concomitant medication (e.g. diuretics).

**Therapeutic range**
Acute mania, 0.5–1.2 mmol/L.
Prophylaxis, 0.4–1 mmol/L. Symptoms of toxicity are common >1.5 mmol/L (>1.2 mmol/L in elderly). Sometimes clinical toxicity can occur at lower concentrations, particularly in those with organic neurological damage or other CNS illness (e.g. epilepsy).

**Patient counseling**

Regular blood tests are important during treatment. Be alert for signs and symptoms of lithium toxicity (e.g. extreme thirst and frequent urination, nausea and vomiting), especially during illness, excessive sweating or low fluid intake; if these occur, stop taking the tablets and seek medical attention immediately.

Take with food. Do not break, crush or chew controlled release lithium tablets, and avoid taking with hot drinks.

Maintain a normal diet with regular salt and fluid intake. Drink more non-alcoholic fluid during hot weather to avoid toxicity.

Avoid sodium bicarbonate in products such as indigestion medicines and 'fruit salts', as they make lithium less effective.

**Practice points**

- Most patients require hospitalisation for acute mania
- As onset of action may be delayed for 6–10 days, consider adding a benzodiazepine or antipsychotic (see Bipolar disorder) in severe mania; use oral agents when possible but supervise compliance carefully, and withdraw after acute mania has resolved
- After resolution, titrate lithium dose (see Dosage) to achieve concentration for prophylaxis; treat for 6–12 months
- Obtain renal and thyroid function tests at baseline, then every 3–6 months; monitor for clinical signs and symptoms of thyroid dysfunction
- For patients with significant cardiac disease, consider an ECG at baseline and at follow-up
- Nephrogenic diabetes insipidus greatly increases risk of lithium toxicity; reassess need for lithium if this develops
- Antidepressants may be used with lithium during the depressive phase of bipolar illness
- Do not stop lithium treatment abruptly; withdraw gradually to avoid relapse.

**Products**

**LITHIUM CARBONATE TABS 400 MG (CAMCOLIT®)**

**04.03 ANTIDEPRESSANT DRUGS**

**MAJOR DEPRESSION**

**Rationale for drug use**

Provide relief from psychological and physical symptoms. Enhance functional capacity. Reduce the likelihood of self-harm or suicide.

**Before starting treatment**

Exclude treatable organic causes (e.g. alcohol/illicit drug misuse, hypothyroidism, corticosteroid use). Consider using a structured assessment tool (e.g. Hamilton Depression Rating Scale) to document extent and nature of signs and symptoms for later assessment of treatment response.

Obtain a baseline ECG and electrolytes if intending to use a TCA in children or if there is pre-existing cardiac disease.

Measure standing and sitting BP, especially if considering use of TCA.

Carefully review all current medications including non-prescription drugs, e.g. St John's Wort, and assess potential for interaction.

**When to start treatment**

Treat depression if accepted diagnostic criteria (see **Diagnostic criteria for major depression**) are fulfilled for >2 weeks.

Although drug treatment is often used first, non-drug therapy is useful and worth considering at this time (see **Other treatment**).

Severe depression (e.g. with serious suicidal behaviour or psychotic features) warrants management by a psychiatrist, often in hospital.

**Diagnostic criteria for major depression**

Pervasive depressed mood (or irritable mood in children) and/or marked loss of interest or pleasure plus 4 or more of the following:

- Marked change in weight or appetite
• Insomnia/hypersomnia nearly every day
• Psychomotor agitation/retardation nearly every day
• Fatigue/loss of energy nearly every day
• Feelings of worthlessness, excessive/inappropriate guilt
• Indecisiveness or diminished concentration
• Feelings of hopelessness
• Thoughts of death, suicidal ideation/attempt.

Factors influencing drug choice
When choosing antidepressant drug therapy consider:
• Previous response to antidepressant therapy, including allergies
• Concurrent medical and psychiatric illnesses, e.g. epilepsy, bipolar disorder
• Adverse effect profile of the drug or drug class, e.g. activating effects of an SSRI may be useful when hypersomnia is a presenting symptom
• Potential for drug interactions
• Toxicity in overdose, as well as the likelihood that the patient will attempt a deliberate overdose.

Drug choice
Approximately half of adult patients with major depression respond to antidepressant treatment (compared with 30% response to placebo), and relapse is relatively common. All antidepressant drugs are approximately equal in efficacy, although individual patient response may vary markedly. Similarly, although the antidepressant classes have different adverse effects, no class is superior in terms of tolerability.

TCAs, SSRIs, controlled release venlafaxine, mirtazapine and moclobemide are all regarded as first line drugs in adults. Nonselective MAOIs are generally reserved for patients with previous good response to them, or when other treatments are ineffective or not tolerated.

Previous response to a drug is a good predictor of response for treatment of later episodes. Some patients with severe or melancholic depression may respond better to TCAs or MAOIs than to SSRIs.

Comparative antidepressant information
Sedation: SSRIs and MAOIs tend to be less sedating than TCAs, mianserin or mirtazapine (which may impair ability to drive or operate machinery).

Need for adjunctive drugs: anxiolytic and sedative/hypnotic drugs are less likely to be needed at the start of treatment with TCAs, mianserin or mirtazapine.

Orthostatic hypotension: least likely with SSRIs, venlafaxine, reboxetine and moclobemide.

Toxicity: TCAs, MAOIs and possibly venlafaxine are more toxic in overdose than other first line antidepressants.

Weight gain: TCAs and mirtazapine are often associated with weight gain.

MAOIs
Phenelzine and tranylcypromine are irreversible, nonselective monoamine oxidase inhibitors which are not used first line because they have serious adverse effects, and interactions with other drugs and food.
Moclobemide, a reversible, selective MAOI, has far less potential for interactions and can be prescribed safely for most people if used within recommended dose range.

MAOIs are generally activating; avoid evening dosing.
Phenelzine and tranylcypromine are toxic in overdose, whereas moclobemide is relatively safe.

SSRIs
Selective serotonin reuptake inhibitors are relatively activating and usually best given as a single daily dose each morning.

Routine use of doses above those recommended rarely increases antidepressant effect unless depression is present with obsessive–compulsive disorder.

Tricyclic antidepressants
Nortriptyline appears to be less sedating, and less likely to cause hypotension or anticholinergic effects, than amitriptyline, dothiepin, doxepin and trimipramine.

TCAs are very toxic in overdose.

Other antidepressants
Venlafaxine, mianserin, reboxetine and mirtazapine have efficacy and tolerability comparable to other antidepressants.
Venlafaxine may increase BP, particularly with high doses.

Other treatment
Psychotherapy: always consider psychotherapy (especially cognitive behavioural therapy) as it significantly
augments treatment of depression with drugs and/or electroconvulsive therapy (ECT). Psychotherapy alone may be effective in mild-to-moderate depression. 
ECT: can provide rapid relief with few adverse effects, but cannot be used if there is raised intracranial pressure or a contraindication to general anaesthesia. After a course of ECT, drug therapy is usually needed to maintain remission. St John’s Wort (Hypericum perforatum)—may be more effective than placebo in mild-to-moderate major depression, however further information is required about efficacy, safety and use of standardised products before it can be accepted as an antidepressant. Discourage people from taking antidepressants with St John’s Wort, because there is a risk of serotonin syndrome and other interactions.

**Treatment regimens**

Begin antidepressants with a low dose, increasing gradually over 2–4 weeks as tolerated (dose escalation may not be needed with SSRIs).

Full antidepressant effects may take 6–8 weeks, but a trend to improvement is often seen within 1–3 weeks. Continue drug treatment for 4–12 months after a single episode of major depression. In recurrent depression, consider continuous maintenance treatment.

After completing a course of treatment, withdraw antidepressants over at least 1–2 weeks.

**Adjuventive treatment**

A carefully planned course of benzodiazepines, zolpidem or zopiclone may help insomnia and/or anxiety in the early phase of antidepressant treatment.

If antidepressant therapy (at appropriate maximum doses) produces only a partial response, augmentation, e.g. with lithium, may improve outcome.

Psychotic depression requires antipsychotic treatment in addition to antidepressants.

**Changing antidepressants**

When changing from one agent to another, consider the need for an antidepressant-free period to prevent adverse effects due to drug interactions, see Table 04-3 Antidepressant changeover guide.

General considerations when changing antidepressants:

- Taper antidepressants slowly to avoid withdrawal symptoms
- When deciding length of changeover, consider clinical urgency; it may be shortened with careful monitoring (e.g. hospital inpatient) if necessary
- TCAs and SSRIs (except fluoxetine), elimination half-lives are about 20–30 hours so after 3–4 days most of the drug will be cleared from the body
- fluoxetine’s long half-life (plus that of its metabolites) means that after it is stopped, a period of weeks is needed before another antidepressant can be started (e.g. 5 weeks before starting MAOI)
- Nonselective, irreversible MAOIs, enzyme inhibition may continue for 2–3 weeks after they are stopped (maintain dietary and drug restrictions for this period)
- Consider the possibility of serotonin syndrome.

**Special cases**

Pregnancy and the puerperium: Treatment of depression during this time is complex and requires careful analysis of risk to both mother and infant. On current evidence TCAs and SSRIs (except paroxetine) are relatively safe; use the lowest effective drug dose. ECT may be used, with appropriate preparation.

Neonatal toxicity or withdrawal symptoms may occur in neonates but are self limited; observe neonates carefully for a few days to identify and, if necessary, treat these.

Breastfeeding: Although TCAs have been used in breastfeeding women for many years there are relatively few published data; this is also the case for all other antidepressants. SSRIs and TCAs seem to have similar safety. Moclobemide passes into breast milk in very low concentrations, but there is little known about safety.

Elderly: May respond more slowly. Consider a lower starting dose with a more gradual increase. Claims that the newer antidepressants are better tolerated in the elderly are not well supported by evidence.

Children and adolescents: An experienced child psychiatrist should supervise treatment.

Antidepressants are not often used first line and are usually used with non-drug therapy as part of a holistic approach. Comorbidities are common in childhood depression and should be managed.

As the first evaluation can have substantial positive impact, consider delaying antidepressant treatment for 1–2 weeks after this.

Regulatory agencies around the world have reviewed the effectiveness and safety of antidepressants (with a focus on SSRIs in depressed children and adolescents). Effectiveness seems to have been overstated and risks understated, particularly the early appearance of suicidal thoughts and behaviour.

TCAs are no better than placebo, and their toxicity in overdose is of concern, as depressed adolescents have high rates of attempted and completed suicide. Perform baseline ECG if considering a TCA.
Refractory depression: Ensure that dose and duration of treatment are adequate, exclude potential underlying causes, and investigate for noncompliance or drug interactions.

True refractory depression may be managed by switching to another antidepressant, or by adding different approaches in psychotherapy, augmentation or ECT.

Avoid using >1 antidepressant drug. There is not enough evidence to support combination antidepressant drug therapy and serious adverse effects may occur because of drug interactions.

**Adverse effects of antidepressants**

**Serotonin syndrome**

Serotonin syndrome may occur with a high dose of a single drug, when >1 serotonergic agents are used together, or when changing antidepressants with an inadequate washout period between drugs. Synaptic serotonin concentration increases, hyperstimulating the serotonin receptors and causing:

- Mental state changes (e.g. confusion, hypomania, agitation)
- Myoclonus/clonus, hyperreflexia, tremor, incoordination
- Shivering, sweating, fever
- Diarrhoea.

**Implicated agents**

Many drugs and classes of drug have been associated with its development, see Table 04-2 Drugs that may contribute to the serotonin syndrome.

Serotonin syndrome warrants stopping implicated agent(s) promptly as it may be serious; deaths have been reported.

**Withdrawal symptoms**

See also Table 04-04 Features of antidepressant withdrawal syndromes

Some people experience withdrawal effects after missing 1 or 2 doses, especially when using drugs with short half-lives (e.g. venlafaxine, paroxetine). Risk factors for withdrawal may include high doses and long treatment course.

At the end of a treatment course, taper antidepressant over several weeks and monitor for withdrawal symptoms to reduce this risk; this may also minimise the likelihood of relapse.

Changing antidepressants usually involves stopping or rapid tapering to minimise disruption to treatment. Educate patients about possible withdrawal effects and adverse effects of new drug (rather than explaining symptoms in terms of relapse or worsening of depression); monitor closely. See also Changing antidepressants.

**Antidepressant toxicity**

SSRIs, reboxetine, mirtazapine, mianserin and moclobemide are probably the least toxic of all antidepressants in overdose.

Venlafaxine is more toxic than the group listed above.

TCAs and MAOIs are the most toxic in overdose; avoid using them if there is a high risk for overdose/suicide.

**Unanswered questions**

It is not known whether previous response to nonselective MAOIs predicts response to moclobemide.

**Practice points**

- Consider non-drug therapy whenever possible
- With the exception of nonselective MAOIs, all antidepressants can be considered as first line choices for some patients
- Avoid TCAs and MAOIs if there is a high risk for overdose; SSRIs are often a better choice
- Ensure that an adequate trial of treatment is given, with attention to dosage and duration of therapy
- Consider potential underlying reasons for poor response (e.g. subtherapeutic dose, noncompliance)
- Avoid combining antidepressants.

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**04.03.01 Tricyclic antidepressants (TCAs)**

**AMITRIPTYLINE, CLOMIPRAMINE, IMIPRAMINE, NORTRIPTYLINE**

**Mode of action**

TCAs inhibit reuptake of noradrenaline and serotonin into presynaptic terminals. Although unrelated to the therapeutic effects of the TCAs, they also block cholinergic, histaminergic, alpha₁-adrenergic and serotonergic receptors. Clomipramine has a greater effect on serotonin transport than other TCAs.

**Indications**

- Major depression
- Some anxiety disorders, eg panic disorder (imipramine)
- Nocturnal enuresis, urge incontinence (amitriptyline, imipramine, nortriptyline)
Adjunct in pain management (amitriptyline, doxepin)
Obsessive–compulsive disorders (clomipramine)
Cataplexy associated with narcolepsy (clomipramine)
ADHD (imipramine, nortriptyline)
Migraine prophylaxis (amitriptyline)

**Contraindications**
Treatment with, or within 14 days of stopping, a MAOI
Treatment with, or within 2 days of stopping, moclobemide

**Specific considerations**
Second or third degree heart block, severe ischaemic heart disease, cardiac instability (e.g. after MI)—adverse effects on conduction (proarrhythmic effects) and heart rate may be significant.
Coronary heart disease: tachycardia, from anticholinergic effects or reflex tachycardia secondary to TCAs, may precipitate or exacerbate angina.
Risk factors for prolonging the QT interval, see Prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination. Manufacturer contraindicates use of clomipramine in congenital long QT syndrome.
Orthostatic hypotension: likely to be exacerbated.
Coronary heart disease: from anticholinergic effects or reflex tachycardia secondary to TCAs, may precipitate or exacerbate angina.
Risk factors for prolonging the QT interval, see Prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination. Manufacturer contraindicates use of clomipramine in congenital long QT syndrome.
Orthostatic hypotension: likely to be exacerbated.

**Adverse effects**
Common: sedation, dry mouth, blurred vision, constipation, weight gain, orthostatic hypotension, urinary hesitancy or retention, reduced GI motility, anticholinergic delirium (particularly in the elderly and in Parkinson’s disease), impotence, loss of libido, other sexual adverse effects, tremor, dizziness, sweating, agitation, insomnia
Infrequent: slowed cardiac conduction, T wave inversion or flattening (particularly at high doses), arrhythmias, sinus tachycardia, nausea, hyperglycaemia, gynaecomastia in males, breast enlargement and galactorrhoea in females, allergic skin reactions, manic episodes
Rare: blood dyscrasias, hepatitis, paralytic ileus, SIADH with hyponatraemia, seizures, prolonged QT interval

**Dosage**
**Amitriptyline**
Major depression
25–75 mg daily, increasing by 25–50 mg every 2–3 days to 75–150 mg daily. Maximum, 300 mg daily.
Adjuvant in pain management: 10–25 mg at night initially and gradually titrate dose up to a maximum of 150 mg at night.

Urinary urge incontinence: 10–25 mg 1–3 times daily.

Nocturnal enuresis
Child 7–10 years, 10–20 mg 30–60 minutes before bedtime.
Child >10 years, 25–50 mg 30–60 minutes before bedtime.

**Clomipramine**
25–75 mg daily, increasing by 25–50 mg every 2–3 days to 75–150 mg daily. Maximum, 300 mg daily.

**Imipramine**
Depression, panic disorder
25–75 mg daily, increasing by 25–50 mg every 2–3 days to 75–150 mg daily. Maximum, 300 mg daily.

ADHD: Child >5 years, 10 mg twice daily, increased slowly as clinically indicated in increments of 0.5 mg/kg to a daily maximum of 3 mg/kg, given in 2–3 divided doses.

Nocturnal enuresis
Child 7–10 years, 10–20 mg 30–60 minutes before bedtime.
Child >10 years, 25–50 mg 30–60 minutes before bedtime.

**Nortriptyline**
25–75 mg daily, increasing by 25–50 mg every 2–3 days to 75–150 mg daily. Maximum, 150 mg daily.

Nocturnal enuresis
Child 7–10 years, 10–20 mg 30–60 minutes before bedtime.
Child >10 years, 25–50 mg 30–60 minutes before bedtime.

**Comparative information**
All TCAs are equally effective in major depression.

Clomipramine has greater serotonergic activity than other TCAs; use special caution if changing to other antidepressants because of greater potential for serotonin syndrome.

Evidence suggests that dothiepin may be more toxic in overdose than other TCAs.

**Patient counselling**
You may get side effects such as blurred vision, drowsiness and dry mouth. They may be troublesome but may lessen or disappear after about 7 days. Discuss any problems with your doctor or pharmacist.

You may feel dizzy on standing when taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.

Avoid driving and operating machinery until you know how you react to the medication and your doctor says that you can.

These drugs may increase the effects of alcohol.

Do not stop taking this medicine suddenly unless your doctor tells you to.

**Practice points**
- check BP (supine and standing) before and after starting treatment and after each dose change
- although adverse effects may appear early, therapeutic response is usually delayed by 2 weeks
- increased suicidal thoughts and behaviour can occur soon after starting antidepressants, particularly in young people; monitor patients frequently and carefully early in treatment
- use high strength TCA tablets and capsules in maintenance treatment only, as overdose with high strength formulations is associated with increased mortality compared with low strengths
- TCAs are not a first line therapy for children or adolescents; consider specialist referral and obtain a baseline ECG in this population
- TCAs are sometimes used as prophylaxis for migraine, but they are not first line agents
- give as a single dose at night to aid compliance; if insomnia develops or daytime anxiolytic effect is desirable, give in 2 or 3 divided doses
- alter dose in increments every 2–3 days as needed
- ECG is useful to monitor for heart block or pre-existing prolonged QT interval in adults <60 years for TCA doses >200 mg daily, and in older patients at doses >100 mg daily
- withdraw TCAs slowly to avoid withdrawal symptoms
**04.03.03 Selective serotonin reuptake inhibitors (SSRIs)**

**CITALOPRAM, FLUOXETINE, FLUVOXAMINE**

**Mode of action**
SSRIs selectively inhibit the presynaptic reuptake of serotonin (5-hydroxytryptamine, 5HT).

**Indications**
- Major depression.
- Obsessive–compulsive disorder (OCD).
- Panic disorder.
- Bulimia nervosa (fluoxetine).
- Premenstrual dysphoric disorder (fluoxetine, sertraline).
- Social phobia (escitalopram, paroxetine, sertraline).
- Generalised anxiety disorder (escitalopram, paroxetine).
- Post-traumatic stress disorder (paroxetine).

**Contraindications**
- Treatment with, or within 14 days of stopping, a MAOI.
- Treatment with, or within 2 days of stopping, moclobemide.

**Specific considerations**
- Epilepsy, reduced seizure threshold: SSRIs may lower seizure threshold; use low doses and titrate slowly.
- Bipolar disorder: all antidepressants may provoke a manic episode when used in people with bipolar disorder. Some patients without a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.
- People at high risk of bleeding (age >80 years or previous upper GI bleeding) or taking drugs known to increase risk of GI bleeding (regular aspirin or NSAIDs): likelihood of serious bleeding may be increased; avoid combinations or monitor clinical course carefully.
- Treatment with drugs that may contribute to the serotonin syndrome (Table 04 -02): likelihood of serotonin syndrome may be increased; avoid combinations or monitor clinical course carefully.
- Hepatic impairment: Halve dose in severe impairment.
- Children: A child psychiatrist should begin treatment. Although fluvoxamine and sertraline have marketed indications in children, other SSRIs do not.
- The TGA review of antidepressants (which focused on SSRIs in depressed children and adolescents) concluded that risks had been understated, particularly the early appearance of suicidal thoughts and behaviour.
- Pregnancy: A recent analysis suggests that paroxetine use in pregnancy may be associated with an increased risk of malformations. All other data indicate that SSRIs do not appear to be associated with increased malformations.
- Neonatal withdrawal has been reported (especially with paroxetine) after maternal use in late pregnancy. Until more information is available, avoid using paroxetine in women of child-bearing potential. (Citalopram, Fluoxetine, Paroxetine) ADEC category C. (Fluvoxamine) ADEC category B2.
- Breastfeeding: Using SSRIs during breastfeeding is appropriate if indicated, with close observation of the infant.

**Adverse effects**
- Common: nausea, agitation, insomnia, drowsiness, tremor, dry mouth, diarrhoea, dizziness, headache, sweating, weakness, anxiety, weight gain or loss, sexual dysfunction, rhinitis, myalgia, rash
- Infrequent: extrapyramidal reactions (including tardive dyskinesia and dystonia), sedation, confusion, palpitations, tachycardia, hypotension, hyponatraemia (as part of SIADH), abnormal platelet aggregation/haemorrhagic
complications (e.g. bruising, epistaxis, purpura)
Rare: elevated liver enzymes, hepatitis, hepatic failure, galactorrhoea, blood dyscrasias, seizures, akathisia, paraesthesia, taste disturbance

**Patient counselling**

Do not drive or operate machinery until you know how this medicine affects you.
Do not stop taking this medicine suddenly unless your doctor tells you to.
Tell all doctors, dentists or pharmacists that you are taking this medicine, as there may be significant interactions with other medicines. Do not use non-prescription medicines or herbal products without discussing these with a pharmacist.

**Practice points**

- SSRIs are less likely to alter ability to drive or operate machinery than TCAs
- In depression, increasing the SSRI dose may not provide further improvement; most people can be maintained with 10 mg escitalopram, 20 mg paroxetine, citalopram or fluoxetine, 50 mg sertraline, or 50–100 mg fluvoxamine, except where some psychiatric comorbidities exist
- Dose for the management of OCD or eating disorders is often higher than that needed for depression or anxiety disorders
- For the management of anxiety disorders (e.g. panic disorder), begin with half the normal starting dose and avoid using high maintenance doses as activating effects may exacerbate anxiety
- When stopping SSRI treatment taper over several weeks to avoid withdrawal symptoms; reduce the daily dose by half no faster than weekly.
- Increased suicidal thoughts and behaviour can occur soon after starting antidepressants, particularly with some SSRIs in young people; monitor patients frequently and carefully early in treatment
- Sexual dysfunction is an adverse effect that may affect compliance

**Dosage**

**CITALOPRAM**

20 mg once daily, gradually increasing after 2–4 weeks if necessary to a maximum of 60 mg daily (40 mg in the elderly) if used for OCD or eating disorders. In major depression, maintenance doses >20 mg are not usually necessary.

**FLUOXETINE**

Major depression: 20 mg once daily, gradually increasing if necessary to 60 mg daily. Use of maintenance doses >20 mg is not usually necessary.

Obessive–compulsive disorder, bulimia nervosa: 20 mg once daily, increasing as indicated to 60–80 mg daily.

Panic disorder: 10 mg daily; do not exceed 20 mg daily.

Premenstrual dysphoric disorder: Continuous treatment, 20 mg once daily. Cyclic treatment, 20 mg once daily starting 14 days before the anticipated start of menstruation until the first full day of menses.

**FLUOXAMINE**

Adult: Initially 50 mg once daily, gradually increasing as necessary to 100–300 mg daily. In depression and panic disorder, doses >100 mg daily are not usually needed. Give doses >150 mg in 2–3 divided doses. Maximum, 300 mg daily.

Obessive–compulsive disorder, child >8 years: 25 mg once daily increasing every 7 days as necessary and if tolerated. Take the size of the child into account when adjusting dose; maximum dose 200 mg daily. Give children doses >50 mg daily in 2 divided doses.

**PAROXETINE**

Major depression: 20 mg once daily, gradually increasing as necessary to a maximum of 50 mg once daily. Use of maintenance doses >20 mg is not routinely necessary.

Generalised anxiety disorder, social phobia, post traumatic stress disorder: Start at 10 mg daily, increasing if necessary by 10 mg after a week to 20 mg once daily. Use of maintenance doses >20 mg is not routinely necessary. Obsessive–compulsive disorder, panic disorder: 20 mg once daily, gradually increasing if needed, up to 50 mg once daily.
04.03.04 Other antidepressant drugs

**MIRTAZAPINE**

**Mode of action**
Post synaptic blockade of serotonin 5HT_{2} and 5HT_{3} receptors, presynaptic blockade of central alpha_{2}-adrenergic inhibitory autoreceptors.

**Indications**
Major depression.

**Contraindications**
Manufacturer contraindicates treatment with, or within 14 days of stopping, a MAOI.

**Specific considerations**
Allergy, intolerance to mianserin: avoid mirtazapine; closely related in structure to mianserin.
Epilepsy, reduced seizure threshold: mirtazapine lowers seizure threshold; use low doses and titrate slowly.
Bipolar disorder: all antidepressants may provoke a manic episode when used in people with bipolar disorder. Some patients without a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.
Treatment with drugs which can contribute to the serotonin syndrome: likelihood of serotonin syndrome may be increased; avoid combinations or monitor clinical course carefully.
Children: Safety and efficacy not established for people <18 years.

**Pregnancy:** ADEC category B3.

**Breastfeeding:** Contact specialised information service.

**Adverse effects**
Common: increased appetite, weight gain, sedation, weakness, peripheral oedema.
Rare: orthostatic hypotension, seizures, mania, rash, granulocytopenia, agranulocytosis.

**Dosage**
15 mg at night, increasing gradually as indicated to 30–45 mg at night, maximum 60 mg.

**Patient counselling**
This medicine may cause drowsiness and may increase the effects of alcohol; do not drive or operate machinery if you are affected.
Do not stop taking this medicine suddenly unless your doctor tells you to.

**Practice points**
- increased suicidal thoughts and behaviour can occur soon after starting antidepressants, particularly in young people; monitor patients frequently and carefully early in treatment
- whenever practical, and especially after completing a course of treatment, withdraw mirtazapine over at least 1–2 weeks, in order to minimise risk of withdrawal symptoms
- sedative action may be useful for depression where insomnia is a feature.

**Products**
MIRTAZAPINE TABS 30 MG (REMERON®)

**VENLAFAXINE**

**Mode of action**
Inhibits serotonin and noradrenaline reuptake.

**Indications**
Major depression, Generalised anxiety disorder, Social phobia.

**Contraindications**
Treatment with, or within 14 days of stopping, a MAOI.
Treatment with, or within 2 days of stopping, moclobemide.

Specific considerations
Hypertension: may be exacerbated by venlafaxine. Manufacturer suggests hypertension be controlled before treatment.
Bipolar disorder: all antidepressants may provoke a manic episode when used in people with bipolar disorder. Some patients without a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.
History of seizures: venlafaxine can cause seizures.
Treatment with drugs which can contribute to the serotonin syndrome: likelihood of serotonin syndrome may be increased; avoid combinations or monitor clinical course carefully.
Renal impairment: Halve dose in severe impairment.
Hepatic impairment: Halve dose in severe impairment.
Children: Do not use, as efficacy and safety are have not been demonstrated in people <18 years.
Pregnancy: Exposure in late pregnancy may result in withdrawal symptoms in newborns. ADEC category B2.
Breastfeeding: Contact specialised information service.

Adverse effects
Common: nausea, vomiting, anorexia, headache, sweating, rash, anxiety, dizziness, fatigue, syncope, hypertension (dose-related), orthostatic hypotension, tremor.
Infrequent: sexual dysfunction (e.g. impotence), loss of libido, dry mouth, insomnia, somnolence, constipation, hyponatraemia, ECG changes, palpitations, hepatitis, seizures.
Rare: skin and mucous membrane bleeding, acute closed angle glaucoma.

Dosage
Although most people will respond to doses of 150 mg daily or less, doses of up to 225 mg daily may be needed in some cases. Little is known about efficacy and safety above 225 mg daily.
Conventional tablet, 37.5 mg twice daily, increasing to 75 mg twice daily if required.
Controlled release capsule, 75 mg once daily, increasing to 150 mg once daily if required.
Renal, hepatic impairment: Conventional tablet, initially 37.5 mg daily; titrate carefully against clinical effects. In some cases controlled release capsules may be suitable.
Maximum: Conventional tablet, up to 375 mg daily in divided doses has been used in severe depression. Controlled release capsule, 300 mg daily.

Patient counselling
Take with food to minimise stomach upsets.
Do not open, crush, or chew controlled release capsules, or put them in water.
Be careful driving or operating machinery until you know how venlafaxine affects you.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
- monitor BP more frequently when starting, periodically thereafter, especially with doses >200 mg daily
- controlled release formulation may improve tolerability and compliance
- increased suicidal thoughts and behaviour can occur soon after starting antidepressants, particularly in young people; monitor patients frequently and carefully early in treatment
- venlafaxine use has been recently restricted in children and adolescents in the UK and USA
- toxic in overdose; ECG changes, arrhythmias and seizures have been reported, with some fatalities
- whenever practical, and especially after completing a course of treatment, withdraw over at least 2 weeks, in order to minimise risk of withdrawal symptoms; some advise decreasing the dose by 10–15% every 4 days.

Products
VENLAFAXINE TABS 75 MG SR (AS HCL) (EFEXOR®, VAXOR®)

04.04 DRUGS FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER
ATTENTION DEFICIT HYPERACTIVITY DISORDER

Rationale for drug use
Symptom relief. Reduce functional impairment in daily life, including home, school and peer relationships.
Minimise long term adverse effects on academic performance, vocational success, social and emotional development.

Before starting treatment
Diagnosis is more reliable if assessment is conducted with multidisciplinary input.
ADHD symptoms can be produced by a range of other disorders for which psychostimulants are not appropriate treatment, e.g. anxiety disorder. Arrange appropriate specialist assessment by a child psychiatrist or paediatrician. Be aware that diagnostic criteria for ADHD are all normal behaviours in preschool children and therefore the child's developmental status needs to be considered. Clinical assessment should consider information from all potentially relevant sources, such as parents, carers, schools and the patient. Impairment must be demonstrated in 2 or more settings.

**When to start treatment**

Consider drug treatment if ADHD symptoms are causing significant functional impairment. Although drug treatment relieves symptoms, long term benefits have not been demonstrated. Non-drug therapy should also be considered.

**Drug choice**

**Psychostimulants**

Regarded as the drug treatment of choice for children with ADHD, where their use often results in immediate and dramatic improvement in impulsive behaviour and task completion. They are less effective in reducing aggressive behaviours. Methylphenidate and dexamphetamine are thought to have equal efficacy, and have a similar range and incidence of adverse effects.

Dexamphetamine and conventional methylphenidate are often given more than once daily. Controlled release methylphenidate allows once daily dosing, reducing the need to dose at school. Up to 30% of patients with ADHD will not respond to, or will not tolerate, the first psychostimulant. This may decrease to 10–20% if the other psychostimulant is tried. Combine drug therapy with psychosocial interventions. Regular review aids titration to optimal dose. Avoid giving psychostimulants after early afternoon, to minimise sleep disturbance.

Some specialists give initial doses once daily to gauge duration of behavioural effect from the minimum effective dose and to help determine the number of doses required per day and their timing.

**Atomoxetine**

Atomoxetine is a non-stimulant drug indicated specifically for ADHD treatment. At present it is not possible to confirm that atomoxetine is either as effective as, or as well tolerated as, psychostimulants. Some experts suggest it be reserved for patients who do not respond to, or are intolerant of, psychostimulants. It has recently been associated with development of suicidal thoughts and behaviours; patients should be closely monitored for emergence of these effects.

**Tricyclic antidepressants**

TCAs are not first line therapy as there is a possible association between their use in children and sudden death, and they are toxic in overdose. If used, obtain an ECG before starting therapy, repeat at steady-state and periodically thereafter.

**Other drug treatment**

Clonidine is a potential treatment for ADHD because of its alpha-adrenergic effects and sedative properties, but evidence for efficacy is inconclusive. It is sometimes inappropriately used to counteract the insomnia resulting from psychostimulants. There are reported deaths in children using this combination. Begin clonidine at low dose, and titrate slowly upwards. Sedation, dry mouth, constipation, hypotension and possible effects on cardiac conduction limit its usefulness. Avoid in children with pre-existing hypotension or cardiac conduction abnormalities. SSRIs have no proven benefit in ADHD and may exacerbate some symptoms. Psychostimulants combined with antidepressants may increase risk of adverse effects and there is no convincing evidence that such combinations are more effective than psychostimulant monotherapy. However, if depression and ADHD coexist, treatment with both a psychostimulant and an SSRI may be undertaken by specialists.

**Other treatment**

Research on psychosocial interventions in ADHD is largely limited to behaviour management strategies, which seem less effective than psychostimulants. Other psychosocial interventions are not well evaluated. Many other interventions for ADHD have been advocated, e.g. dietary replacement, exclusion or supplementation; various vitamin, mineral or herbal regimens; biofeedback; perceptual stimulation. There is no evidence for these approaches.

**Special cases**

Coexisting tic disorders or Tourette's syndrome are exacerbated by psychostimulants in about 30% of patients so careful clinical monitoring is needed.

**Adult ADHD**

There is no consensus on diagnostic criteria for adult ADHD. A history of ADHD in childhood is generally agreed to
be essential for diagnosis. Other psychiatric conditions often coexist. 
Adults seem to respond to the same treatments as children. 
Dosing of psychostimulants may be tailored to need (e.g. restricted to times of high cognitive demand). 

**Unanswered Questions**
ADHD can be subdivided into inattentive, hyperactive-impulsive and combination subtypes. There are more data to guide treatment for the combination subtype than for the inattentive or hyperactive-impulsive subtypes. 
There are no conclusive data to establish unequivocal treatment guidelines for older adolescents and adults with ADHD. 
Information about effects of long term treatment (>1 year) is insufficient, and there is no evidence that long term learning outcomes are improved.

**Practice points**
- response to psychostimulants is commonly rapid and striking; do not continue treatment if there is no benefit after optimal treatment
- although some children may have diminished growth velocity and weight loss during psychostimulant treatment, the overall long term effect is thought to be insignificant in most cases; monitor weight and height, and if concerned, use drug-free holidays or alternative therapy
- atomoxetine may also retard height and weight growth velocity slightly and has recently been associated with an increased risk of suicidality
- at present there are no clear recommendations on appropriate duration of treatment.

**METHYLPHENIDATE**

**Mode of action**
Methylphenidate is thought to enhance noradrenergic and dopaminergic neurotransmission in ADHD.

**Indications**
Attention deficit hyperactivity disorder, Narcolepsy.

**Contraindications**
Substance misuse.
Acute psychotic disorder.
Drug diversion by parents/carers/siblings.
Treatment with, or within 14 days of stopping, a MAOI.

**Specific considerations**
Tic disorders, Tourette's syndrome: may worsen; monitor closely or consider alternative treatment, e.g. clonidine.
Angina, arrhythmia, hyperthyroidism, glaucoma, anxiety, agitation: may worsen; use with care and seek specialist advice.
Hepatic impairment: Halve dose in severe impairment.
Pregnancy: Management of ADHD in pregnant women should only be undertaken with specialist guidance; ADEC category B2.
Breastfeeding: Seek specialist advice.

**Adverse effects**
Most adverse effects of methylphenidate are dose-dependent.
Common: nausea, loss of appetite, anxiety, insomnia, dry mouth.
Infrequent: movement disorders, tics, rash, weight loss, growth retardation.
Rare: psychosis, neuroleptic malignant syndrome, liver dysfunction.

**Dosage**

**ADHD**

School-age child
Use conventional tablets to begin treatment; controlled release products may not be suitable to start treatment in all children because of the doses available.
Conventional tablet, start at 5–10 mg daily given in 1–2 doses, increasing by 5–10 mg/day each week to a maximum of 40 mg/day. When total daily dose is >10 mg give in 2–3 doses, or consider swapping to a controlled release product.

Adult
Initially 10 mg each morning; increase at weekly intervals as clinically indicated by 5–10 mg/day given in divided doses. Maximum 60 mg/day.

**Narcolepsy**
Adult, initially 5 mg twice daily (morning and noon); gradually increase to 20–30 mg daily given in divided doses.
Maximum 60 mg/day.

**Patient counselling**
Avoid taking doses after early afternoon if you have trouble sleeping at night (this may make you feel drowsy next day). This medicine may also make you feel dizzy; do not drive or operate machinery if you are affected.

**Practice points**
- Prescription of methylphenidate is subject to specific State/Territory laws relating to narcotic and psychotropic drugs
- Supply of controlled release is not subsidised through the PBS
- Do not continue methylphenidate if there is no benefit after optimal treatment

**Products**
METHYLPHENIDATE TABS 10 MG (AS HCL) (RITALIN®)

## 04.07 ANALGESICS

**PAIN MANAGEMENT**
Pain has a complex aetiology involving not just physical disorders, but also pathological, physiological, psychological, cognitive and environmental factors.

It may be classified clinically as:
- nociceptive: due to activation of normal pain fibres; may be somatic (e.g. involving superficial structures such as skin and muscle) or visceral (e.g. involving deeper organs such as liver, pancreas).
- neuropathic: due to nerve injury, disease or surgical section occurring anywhere in the pain pathway from peripheral (e.g. post-herpetic neuralgia, diabetic neuropathy, phantom limb) to central (e.g. spinal cord injury, post stroke), including the autonomic nervous system.
- mixed nociceptive/neuropathic.

It may also be described as:
- acute pain: recent onset, usually of short duration; the cause is often identifiable, e.g. disease, trauma
- chronic pain: persists for >3 months or persists after healing is expected to be complete; it is often further classified into cancer or non-cancer pain; acute exacerbations of chronic pain may occur
- breakthrough pain: occurs between doses of drugs in patients receiving regular analgesia
- incident pain: occurs on, or is exacerbated by, movement.

**Approach to management**
Pain is best treated early and effectively because, once established, it is more difficult to treat. In addition, there is increasing clinical evidence that appropriate early, aggressive management of acute pain may minimise the transition to chronic pain.

An integrated multidisciplinary approach to pain management is often required for both acute and chronic pain. Patient involvement in the initial and continuing assessment of their pain and their response to treatment is essential. Multimodal management is common and has been shown to be effective. This includes use of analgesic drugs, local anaesthetic techniques (e.g. nerve blocks, epidural or intrathecal analgesia), disease-specific treatments (e.g. chemotherapy, radiotherapy or surgery when appropriate), together with non-drug techniques and attention to psychosocial issues.

**Assessment of pain**
Aim to:
- identify the pain mechanism
- detect acute pain syndromes (e.g. acute herpes zoster, inflammatory arthropathy) and warning signs indicating serious underlying pathology or features that predict the possibility of progression to chronic pain
- measure pain severity
- document drug and alcohol history
- develop a management plan including regular follow-up; review plan at specific intervals.

**Measurement of pain severity**
Pain is a subjective experience and cannot be measured directly. Patient self-reporting is the best way to assess pain. When measurements are taken using reliable methods (see below) the results are sensitive and consistent. In some situations (e.g. young children, cognitive impairment, psychiatric pathology) such techniques are not possible and observer assessment of non-verbal behaviour is then necessary. Once a scale has been selected for an individual, continue to use this for monitoring pain intensity.

Some commonly used and validated measurement methods are:
• numerical rating scale, rates pain on a scale from 0 (no pain) to 10 (worst pain imaginable).
• Verbal (categorical) rating scales, use words to describe the pain, e.g. none, mild, moderate, severe, worst possible.
• visual analogue scales, e.g. 10 cm unmarked line with 'no pain' at the left end to 'worst pain imaginable' at the right end.
• wong-Baker FACES pain rating scale

For acute pain, using a scale provides a way of monitoring pain intensity and treatment response. For chronic pain, additional psychosocial and functional assessments as well as more complex measures of pain (e.g. Magill Pain Questionnaire) will be necessary.

**Non-drug treatment**

This includes cognitive behavioural therapies, heat or cold applications, massage, exercise, immobilisation, transcutaneous electrical nerve stimulation (TENS). Cognitive behavioural therapies, relaxation techniques and massage are beneficial in chronic pain, but evidence for their efficacy and that of other non-drug methods in acute pain management is inconclusive. Surgery and invasive procedures including neural blockade or spinal cord stimulation are other options.

**Drug choice**

Appropriate prescribing depends on tailoring the analgesia to the mechanism and severity of pain, as well as to the patient. Drug treatment of pain needs to be flexible and individualised. Adequate pain relief is more important than strict adherence to a fixed regimen.

The WHO analgesic ladder for cancer pain is often also used for acute and chronic non-cancer pain. It provides a simple approach to pain management, starting with a non-opioid and moving up to potent opioids. Treatment starts at the step appropriate for the severity of the pain.

The approach to pain management is becoming more mechanistic, based on recognising and modifying the mechanisms involved in the initiation and maintenance of pain (see Pain mechanism). Combination drug therapy using different classes of analgesics may be required.

The duration of action of an analgesic and/or the timing of administration can influence the choice of drug. For example, a short acting agent is useful for acute, infrequent or incident pain and is often more effective when given before predictable pain, e.g. dressing a wound. A long acting analgesic is suitable for persistent or frequently recurring pain.

The choice of drugs includes paracetamol, NSAIDs, opioids, local anaesthetics, ketamine, clonidine and adjuvant agents such as antidepressants, antiepileptics, mexiletine and corticosteroids.

**Factors influencing drug selection**

**Pain mechanism**

Knowledge of anatomical and pathophysiological origins of pain (e.g. bone metastases, nerve root compression/infiltration or postoperative) may assist in drug choice. However, this approach is not suitable for all pain types. Drugs which target specific neuroreceptors and neurochemicals (e.g. sodium channels, N-methyl-D-aspartate receptors) may also be used, particularly in neuropathic pain.

See Table 04-05 Pain types and analgesia

**Age**

Children (of all ages) and adults experience similar types of pain and the principles of pain management, including drug treatment, apply to all individuals.

Children: Avoid painful routes of drug administration where possible. Non-drug strategies including distraction, hypnosis and comfort (e.g. cuddling, swaddling) are used in addition to analgesia to manage acute procedural pain.

Techniques such as patient controlled analgesia (PCA) can be used in hospital for children >5 years and use of local analgesia (including topical, epidural, nerve blocks) has become more widespread.

Elderly: Usually require lower doses of analgesics because of altered pharmacokinetics and pharmacodynamics.

NSAIDs, including selective COX-2 inhibitors, should only be used with extreme caution. Paracetamol and/or low dose opioids are generally preferred.

**Route of administration**

Oral

Use the oral route where possible. If allowance is made for bioavailability differences, the oral route is as effective as parenteral administration in most cases.

The type of pain determines the appropriate formulation. Controlled release preparations are useful for stable chronic pain, but are not suitable for rapid titration of acute pain relief because of slow onset of effect.

Use an immediate release formulation for acute pain, dose titration (initial treatment and unstable pain phases), and for breakthrough and incident pain in patients on a stable dosage of analgesic. Soluble or effervescent preparations
may have a more rapid onset of effect compared with conventional tablets or capsules.
Transmucosal lozenges have a rapid effect and are also appropriate for the relief of breakthrough pain.

Parenteral
Consider parenteral administration if the patient is unable to swallow, suffers excessive nausea and vomiting or has delayed gastric emptying (e.g. intestinal obstruction).
IV administration is preferred for acute, severe pain, e.g. postoperatively, but is not appropriate for chronic pain.
SC administration is minimally invasive and is as effective as the IV route. It is used for intermittent doses and infusions of opioids in acute and chronic pain. Intermittent SC injections should be given over 1–2 minutes to minimise discomfort.
IM administration is painful and absorption may be erratic. It has no role in cancer pain relief and is becoming less common in managing other types of pain.
Both SC and IM routes of analgesia are contraindicated in major burns.
PCA by IV or SC routes gives greater patient satisfaction and better relief of postoperative pain than conventional methods of administration. However, it requires special infusion pumps and education of patients and staff.

Other routes
The rectal route is another alternative if the patient is unable to take medication by mouth.
Transdermal patches provide continuous systemic dosage of highly lipid soluble drugs such as fentanyl. They are appropriate for stable chronic pain although the dosage is relatively inflexible. Because the onset of effect is very slow and the risk of overdosage in opioid-naïve patients is high, they are not suitable for treatment of acute pain and are not recommended in opioid-naïve patients with chronic non-cancer pain. After removal of the patch, monitor for adverse effects for up to 24 hours.
Inhaled drugs, e.g. nitrous oxide or methoxyflurane, may be useful in some painful situations, including labour and delivery, dressing changes and during ambulance transport of patients.
Epidural, intrathecal or regional nerve blockade are effective for acute pain management but require additional monitoring, equipment and staff education. Safety is equivalent to traditional analgesic methods when coordinated by an acute pain service.

**ACUTE PAIN**
Acute pain often has a defined pattern of onset, site, character and duration. It is commonly associated with trauma, acute medical illness, childbirth and surgery.

**Rationale for drug use**
Relieve suffering.
Reduce or prevent harmful physiological and psychological effects.
Reduce transition to chronic pain.
Assist rehabilitation by physical therapy and mobilisation.

**Before starting treatment**
Identify precipitating cause if possible; this must not delay administration of adequate analgesia.

**When to start treatment**
As soon as possible. When pain is predictable, e.g. postoperatively, prophylaxis is appropriate.

**Drug choice**
In general, opioids are the drugs of choice for severe acute pain. The key principle is to titrate the dose against pain relief, minimising unwanted effects. The dose of opioid required may vary 8- to 10-fold between patients of similar age, irrespective of weight.
The IV route is the most efficacious for severe acute pain and is preferred where adequate staffing and monitoring are available; IM (least desirable) or SC routes can be used.
Oral analgesics (e.g. paracetamol, NSAIDs) alone or with opioids, may also be appropriate if the patient can drink and swallow, but have a slower onset of effect.

**Special cases**

**Postoperative pain**
Aim for early control and regular assessment, as postoperative pain tends to change with time. Even minor surgery can be associated with substantial pain which may last up to a week and interfere with activities of daily living.
Multimodal analgesia aims to increase pain relief while minimising adverse effects. The severity of opioid adverse effects correlates with increased length of hospital stay, delay in returning to normal activity and patient dissatisfaction with analgesics. Adding non-opioid analgesics, including NSAIDs, paracetamol, local anaesthetics, ketamine and clonidine, may have an opioid-sparing effect.
An 'as required' regimen, where the dose of analgesic is titrated to the patient's response, is often appropriate. In addition, prevent pain by giving regular paracetamol and/or NSAIDs (often with opioids as required).
NSAIDs and/or paracetamol may be adequate after minor and day case procedures. Codeine 60 mg added to paracetamol produces additional pain relief even as a single dose. Lower doses of codeine may be subtherapeutic while still causing adverse effects, e.g. constipation. The oral route is not usually suitable immediately after major surgery. Rectal administration is an alternative. IV administration using patient-controlled analgesia (PCA) can provide reliable analgesia and increased patient satisfaction. Epidural analgesia, using a combination of opioid and local anaesthetic is effective after major surgery. It may reduce postoperative morbidity and hospital stay. Patient-controlled epidural analgesia (PCEA) is used in some centres and appears promising. Other interventions that can be effective for specific surgical procedures include intrathecal opioids, peripheral nerve blocks, field blocks, wound infiltration and intra-articular opioids.

**Labour pain**

Regional blockade

Epidural or intrathecal analgesia, either alone or in combination, using a local anaesthetic or an opioid (usually fentanyl, occasionally morphine or pethidine) or both, provides the most effective pain relief during labour. The combination of opioid and local anaesthetic improves pain relief, thereby reducing the required dose and adverse effects associated with use of either alone. After the initial dose, epidural analgesia can be extended with intermittent top-ups by continuous infusion or by patient-controlled techniques.

**Less effective options**

Nitrous oxide and oxygen: a 50:50 mixture is self-administered

IV PCA: may be useful when placement of an epidural catheter is contraindicated (fentanyl is drug of choice; remifentanil also suitable)

Intermittent IV or IM opioids (pethidine or morphine): are decreasing in popularity because of the high frequency of maternal and neonatal adverse effects and limited evidence for their efficacy

non-drug methods: of the methods commonly used, relaxation and massage appear to be more effective than transcutaneous electrical nerve stimulation (TENS) or warm water baths.

**Renal colic**

NSAIDs and opioids provide effective pain relief, particularly if given parenterally. Unless contraindicated, use NSAID as first line treatment owing to the high rate of vomiting associated with opioids. Where an opioid analgesic is required, morphine is preferred.

**Biliary colic**

Parenteral NSAIDs and opioids appear to have similar efficacy in relieving pain. All opioids, including pethidine and morphine, may cause spasm of the sphincter of Oddi; there is little difference in their clinical effect.

**Acute abdomen**

Early administration of opioids in adults and children with an 'acute abdomen' does not reduce the detection rate of serious pathology but may actually facilitate it. Give appropriate analgesia to such patients.

**Acute herpes zoster**

Antiviral agents (see Guanine analogues) relieve the acute pain and decrease the risk of post-herpetic neuralgia if given within 72 hours of onset of rash. Opioids may be necessary for relief of severe pain. Amitriptyline is also used and may reduce the duration of pain.

**Acute back pain**

Advise patient to continue ordinary activity, to avoid bed rest and to use paracetamol or short term NSAIDs. Although evidence for the efficacy of paracetamol in this condition is lacking, it is beneficial in other types of acute musculoskeletal pain. NSAIDs are effective, but adverse effects are common with long term use. The analgesic effect of opioids and combination analgesics is similar to NSAIDs, but even short term use of opioids can be associated with adverse effects.

There is conflicting evidence about the place of muscle relaxants (e.g. baclofen, diazepam) in the treatment of acute back pain and adverse effects are common. Behavioural therapy may be beneficial, but evidence for the efficacy of other non-drug interventions (e.g. back exercises, spinal manipulation, massage, acupuncture, lumbar support) in acute back pain is either lacking or inconclusive.

**Practice points**

- consider the possibility of undetected pathology or the development of other problems if pain:
  - responds poorly to appropriate management
  - changes in pattern
increases in severity
- is becoming chronic

- whether analgesia is given before or after the surgical incision does not affect the degree of pain relief after surgery
- although pain relief alone is beneficial in the short term, evidence of the effect on overall outcome (time to discharge and length of hospital stay) after moderate to major surgery is inconclusive; a multidisciplinary approach (including effective analgesia) with an emphasis on rehabilitation is necessary for improved functional recovery.

**CHRONIC PAIN**
Management requires understanding of physical, emotional, cognitive and psychosocial factors, and use of multiple treatment strategies. Drug treatment is not always appropriate.

Chronic pain includes cancer pain and non-cancer pain.

**Rationale for drug use**
Provide symptom relief.
Maintain or restore function.
Improve quality of life.

**Before starting treatment**
Treat identifiable pathology if possible.
Discuss and agree on realistic treatment goals with the patient and carer. Acceptable outcomes may vary depending on the nature of the pain and the patient. It is not usually possible to eliminate pain completely but it should be possible to reduce symptoms to a tolerable level. Minimising adverse drug effects and maintaining or restoring function are also important considerations.

In cancer pain, the focus is on alleviating symptoms even if function is decreased. In non-cancer pain, the main aim is to improve function with less emphasis on symptom control.

People with a history of substance misuse should not be denied treatment. Their pain should be managed effectively and higher doses of analgesics may be required. Liaise with local drug and alcohol services regarding their care.

**Common management issues**
Give drugs orally unless there is an impediment or contraindication to swallowing, a need for rapid pain control or a specific need for a parenteral route.
After initial titration and stabilisation, give analgesics at regular intervals to allow continuous pain relief.
Rationalise current drug treatment where possible as patients are often taking many drugs.
Titrate dosages against patient response and adverse effects, and review regularly. Fear of adverse effects of analgesics is often disproportionate to actual risk and should not result in undertreatment. However, long term use of NSAIDs is associated with a significant incidence of serious problems, particularly in the elderly (see Adverse effects in NSAIDs).
Ensure early referral of patients who fail to obtain adequate pain relief to a multidisciplinary pain clinic or palliative care service.

**Breakthrough and incident pain**
Breakthrough pain is managed primarily with short acting oral or transmucosal opioids. Onset of effect is approximately 30 minutes for oral morphine liquid and within 15 minutes for fentanyl lozenge.
Incident pain can be difficult to manage because the level of analgesia necessary to control movement-related pain leads to unacceptable adverse effects at rest. When it is predictable (e.g. bathing, dressing) the options are:
- short acting opioid half an hour before painful activity (see Opioid analgesics)
- NSAIDs half an hour before painful activity
- nitrous oxide and oxygen just before/during movement.

**Neuropathic pain**
TCAs and antiepileptics are considered to be the drug treatments of choice, but recent evidence has established that opioids (e.g. morphine, oxycodone, tramadol, methadone) are effective in relieving neuropathic pain, particularly in peripheral pain syndromes. Other agents, such as lignocaine (systemic and topical), mexiletine, ketamine, clonidine and topical capsaicin, may be beneficial in some cases.
There is little evidence of any difference in efficacy between tricyclic antidepressants and their use may be limited by adverse effects, particularly among the elderly. Nortriptyline provides equivalent analgesia but is better tolerated than amitriptyline.
SSRIs and other antidepressants (e.g. venlafaxine) do not appear as effective as TCAs in relieving neuropathic pain, but have a lower incidence of adverse effects.
Antiepileptics for which there is strong evidence of efficacy include carbamazepine (particularly for trigeminal neuralgia) and gabapentin. Of these, gabapentin has a relatively favourable adverse effect profile and minimal drug interactions. Other antiepileptics (e.g. valproate, oxcarbazepine, lamotrigine, pregabalin, topiramate) may be useful in certain neuropathic conditions, but further evaluation of effectiveness is required. Even within a drug class, some patients who fail to respond to 1 medication will respond to another. Although data to support the use of combination therapy are lacking, specialists often use 2 or more drugs that target different sites in the pain pathway.

**Cancer pain**

Can be controlled using the WHO analgesic ladder in >80% of patients. For the remainder a multimodal approach is required.

Choose treatment according to the severity, type and cause of pain.

- **Mild pain:** regular paracetamol or NSAID. The choice depends on a risk/benefit analysis for each patient.
- **Moderate pain:** add tramadol, codeine or dextropropoxyphene (least desirable) to non-opioid; prescribe separately to give flexibility in dose adjustment and in the selection of the most appropriate combination.
- **Severe pain:** add other opioid to non-opioid; morphine is opioid of choice for oral use; if not tolerated use oxycodone, hydromorphone, fentanyl or methadone (see Opioid analgesics).

No pain is predictably unresponsive to opioids; all patients with cancer pain unresponsive to other measures should receive a trial of opioid analgesia.

In cancer pain, addiction is rare; fear of this problem should not prevent early prescription and use of opioid medication. For definition of addiction, see Opioids in non-cancer pain.

Analgesia and adverse effects may sometimes be improved by changing the opioid, but specialist advice is recommended. Once adequate pain control is achieved with conventional release preparations, consider conversion to controlled release formulations.

Adjuvant analgesics such as TCAs, antiepileptics, local anaesthetics, clonidine and ketamine are used with non-opioid/opioid treatment for additional pain relief. Ketamine may be used in low dose SC/IV infusion for pain unresponsive to other agents.

**Metastatic bone pain**

Radiotherapy is the treatment of choice for localised bone pain. For widespread bone pain NSAIDs, bisphosphonates, dexamethasone, and radioactive strontium-89 can be used. Bisphosphonates have a slow onset of effect and may transiently increase pain; they are effective in multiple myeloma and bone metastases from breast cancer, and may also reduce pain associated with other bone metastases. Consider radioactive strontium-89 for pain due to widespread bone metastases from prostatic cancer.

**Pain due to inflammation and oedema in confined spaces**

Examples include raised intracranial pressure, hepatic capsular pain, nerve compression or infiltration. Consider a therapeutic trial of corticosteroid. Dexamethasone is preferred as it is potent and causes less sodium retention; high doses may be required.

**Other causes of pain in cancer**

Pain due to bowel colic may be treated with antispasmodics and opioid antidiarrhoeal; consider stimulant laxatives as possible contributory factors. See Hyoscine butylbromide, Diphenoxylate, Loperamide.

Muscle spasm may be relieved by muscle relaxants (see Baclofen, Diazepam).

**Non-cancer pain**

Reassure the patient and family and address any misunderstandings about the cause of pain, and their expectations regarding its management. Education and motivation of the patient are important to improve compliance. Individualise treatment and assess patients regularly.

Use drugs only as part of an integrated, multidisciplinary strategy to improve physical and social function.

**Opioids in non-cancer pain**

Reserve opioids for pain unresponsive to other drug and non-drug treatments.

Involve a specialist pain team in assessing and managing these patients. The likelihood of benefit from opioids needs to be weighed against the potential for their misuse in each case.

Use of opioids for chronic non-cancer pain may also be associated with concerns regarding effectiveness, adverse effects, tolerance and addiction:

- evidence for efficacy in improving quality of life and function is scarce
- adverse effects:
  - nausea and vomiting improve within the first few days in most patients
  - constipation persists and laxatives are needed for as long as opioids are used
the cognitive effects of long term opioid use are less clear; driving skills do not appear to be affected but in the elderly there is an increased risk of falls

- tolerance to the analgesic effect is uncommon; a stable dose can usually be achieved in responsive patients
- dependence:
  - physical dependence (withdrawal syndrome when the drug is stopped suddenly or an antagonist is given) is common
  - the risk of psychological dependence (a compulsion to use the drug) and addiction (compulsive use to the detriment of physical and/or psychological and/or social function) developing in patients without a history of substance misuse is unknown, but is probably low
  - to minimise the risk, only 1 doctor should prescribe opioids and assess the response regularly.

Data comparing long acting opioids with each other and with short acting opioids in chronic non-cancer pain are lacking; there is also a lack of information on the long term effects of medically prescribed opioids.

Inform patients fully of their responsibilities and the potential consequences of this treatment and obtain written consent.

Before prescribing opioids on a long term basis, conduct a trial over 4–6 weeks. Agree on criteria (e.g. function, quality of life) for success or failure with the patient. If the expected outcomes have not been achieved at the end of the trial period, taper the dose over a few days before stopping the drug.

Start treatment with the equivalent of controlled release morphine 5–30 mg twice daily and adjust dose according to the response after 1 week or less. Use regular (by the clock) dosing. As a rule, avoid short acting preparations.

Review weekly at first and then monthly. The optimum dose is determined by the balance between benefit and adverse effects. If there are unacceptable adverse effects or inadequate pain control, consider gradual opioid withdrawal. Patients must be advised not to stop their medication abruptly because of risk of withdrawal symptoms.

**Chronic back pain**

Identify treatable causes. Advise patient to stay active.

Paracetamol and NSAIDs may provide short term pain relief, but evidence of effectiveness with long term use is lacking.

TCAs, e.g. amitriptyline, are more effective than placebo in relieving pain, but do not consistently improve function or depression. Their use for >8 weeks has not been established and their role in chronic back pain remains controversial. However, a trial of treatment may be useful.

There is insufficient evidence regarding the benefits of muscle relaxants in chronic back pain. Adverse effects are frequent, a strong likelihood of dependency exists, and efficacy compared with analgesics is unknown.

Opioids are only partially effective in relieving pain, and are unlikely to improve psychological or functional status. In some cases, however, a short course of oral opioid (<1 week) may assist early mobilisation.

Massage reduces pain and improves function and other interventions such as exercise therapy or behavioural therapy may be beneficial, particularly in the context of multidisciplinary treatment.

**Practice points**

- If needed, adjust the dose of controlled release opioids, not the frequency of administration.

**04.07.01 Non-opioid analgesics**

Non-opioid analgesics are a chemically diverse group of drugs including NSAIDs and paracetamol. NSAIDs also have anti-inflammatory, antipyretic and antiplatelet properties; paracetamol has an antipyretic action, minimal anti-inflammatory effects, and no effect on platelets.

Paracetamol is preferred to NSAIDs for fever and mild-to-moderate pain as it has fewer adverse effects.

**Combination analgesics**

Avoid products containing aspirin or paracetamol with a non-analgesic, e.g. Norgesic® (contains orphenadrine), Mersyndol® (contains doxylamine). Preparations containing sedating antihistamines may have some added hypnotic effect but no additional analgesic effect.

Problems with combination analgesics include:

- fixed combinations do not allow titration of doses of components
- accumulation of the drug with the longer half-life where the combination contains drugs with different half-lives, e.g. dextropropoxyphene and paracetamol
- increased likelihood of adverse effects including analgesic nephropathy
- potential misuse of opioid-containing combinations
- often more expensive.
ACETYLSALICYLIC ACID
Also known as Aspirin.

**Mode of action**
Aspirin has analgesic, anti-inflammatory, antipyretic and antiplatelet actions. It is a nonselective NSAID, preventing synthesis of prostaglandins by noncompetitively inhibiting both forms of cyclo-oxygenase (COX), COX-1 and COX-2.

**Indications**
Inhibition of platelet aggregation.
Symptomatic relief of:
Fever (>18 years of age), Mild-to-moderate pain due to inflammation and tissue injury, Migraine and tension headache, Period pain, Metastatic bone pain, Rheumatoid arthritis, including juvenile rheumatoid arthritis.
Osteoarthritis, Rheumatic disorders, including acute rheumatic fever.
Combination with codeine—mild to moderate pain.

**Contraindications**
Active peptic ulcer disease.
Allergic reaction to aspirin or other NSAID.
Haemophilia or other bleeding disorder.

**Specific considerations**
Heart failure, uncontrolled hypertension: may be exacerbated by sodium and fluid retention caused by aspirin-induced reduction in glomerular filtration rate and renal blood flow.
Asthma: risk of bronchospasm is increased in patients with aspirin-precipitated asthma.
Intrathecal or epidural analgesia or anaesthesia, or lumbar puncture: avoid use; risk of epidural haematoma which may cause paralysis; if procedure considered necessary, seek specialist advice.
History of peptic ulcer—increased risk of GI ulceration.
G6PD deficiency: doses of up to 1 g daily are tolerated in most people.
Renal impairment: GI symptoms and bleeding diathesis may be worsened. In moderate-to-severe renal impairment, increase dosage interval. Avoid doses >300 mg daily in severe renal impairment; antiplatelet doses of aspirin (<150 mg/day) are considered safe.
Hepatic impairment: Use with caution in severe impairment; increased risk of bleeding.
Surgery: Aspirin's antiplatelet effect lasts for the life of the platelet, if possible, stop aspirin at least 7 days before surgery. There is a risk of renal impairment after surgery, especially if dehydration or renal hypoperfusion exists.
Elderly: Increased risk of adverse effects, in particular GI ulceration and renal impairment.
Children: Avoid use for treatment of fever and muscle ache associated with viral illness in children <18 years, as there is a risk of Reye's syndrome. May be used for rheumatic fever, juvenile chronic arthritis and Kawasaki's disease.
Monitor plasma salicylate concentrations at high doses.

Pregnancy: There is controversy about a possible link between NSAID use during early pregnancy and an increased rate of miscarriage. Aspirin and other NSAIDs inhibit prostaglandin synthesis and when given during the latter part of pregnancy may cause: closure of the fetal ductus arteriosus, fetal renal impairment (which may decrease amniotic fluid volume), inhibition of platelet aggregation, bleeding complications in the newborn and may delay labour and birth. Continuous treatment during the last trimester should only be given on specialist advice. Antiplatelet doses of aspirin (<150 mg/day) are considered safe; ADEC category C.
Breastfeeding Avoid due to theoretical risk of Reye's syndrome; ibuprofen is preferred.

**Adverse effects**
Common: nausea, dyspepsia, vomiting, GI ulceration or bleeding, asymptomatic blood loss, increased bleeding time, headache, dizziness, tinnitus (common with high doses).
Infrequent: skin reactions including erythema multiforme, iron deficiency anaemia, renal impairment, oesophageal ulceration.
Rare: major haemorrhage (GI or other), blood dyscrasias, Bronchospasm, angioedema, urticaria and rhinitis. Allergy have been precipitated by aspirin, particularly in people with asthma; there is cross-reactivity with other NSAIDs.
REYE'S SYNDROME: Do not use aspirin in children <18 years unless specifically indicated. Reye's syndrome with subsequent encephalopathy and severe hepatic injury has been associated with aspirin use in children.

**Dosage**
**Adult**
Analgesic, anti-inflammatory, antipyretic, 300–900 mg every 4–6 hours when necessary.
Moderate-to-severe renal impairment: Increase dosage interval by a factor of 1.5–3.
Severe renal impairment: Do not exceed 300 mg daily.
Child: Rheumatic fever, juvenile chronic arthritis, initially, 15–20 mg/kg every 6 hours; maintenance, 20 mg/kg
every 4–6 hours.
Kawasaki's disease, 10 mg/kg every 8 hours until fever settles, then 3–5 mg/kg once daily.

**Patient counselling**
If you develop swollen ankles, difficulty in breathing, black stools or vomit that looks like coffee grounds, stop taking the medicine and contact your doctor without delay.
Remove tablets or capsules from packaging only immediately before use, as aspirin can break down rapidly if it is not protected by the packaging.
It may be advisable to stop taking aspirin 7 days before planned surgery and some dental procedures; discuss with your doctor or dentist.

**Practice points**
- monitor for GI bleeding, renal failure or hepatic dysfunction in chronic use
- risk of GI bleeding or ulceration is increased if given with corticosteroids
- enteric coated formulations do not reduce the risk of GI ulceration.

**Products**
- ACETYL SALICYLIC ACID TABS 100 MG (ASPIRIN®, ADIPRIN EC®, ASPINORE B®, ASRIVO®, SALISAL E.C®)
- ACETYL SALICYLIC ACID TABS 325 MG (BUFFERED) (BUFFERIN®)

**PARACETAMOL**
Also known as acetaminophen.

**Mode of action**
Not fully determined. Its analgesic effect may be due to inhibition of prostaglandin synthesis centrally, and to a lesser extent peripherally, where other mechanisms which block pain impulses may be involved. The antipyretic effect is probably due to reduced production of prostaglandins in the hypothalamus. Paracetamol has negligible anti-inflammatory effects.

**Indications**
Mild-to-moderate pain, Fever, Migraine and tension headache.

**Combination with codeine**
Pain relief
Fever

**Combination with dextropropoxyphene**
Mild-to-moderate pain (see Dextropropoxyphene)

**Combination with metoclopramide**
Relief of migraine

**Specific considerations**
Renal impairment: There is weak evidence that chronic paracetamol use may increase the rate of progression to chronic renal failure. However, in patients with renal impairment, short term use of paracetamol is safer than NSAIDs (including selective COX-2 inhibitors).
Hepatic impairment: Patients with chronic liver disease may be at increased risk of liver damage following therapeutic dose or overdose of paracetamol, although evidence is lacking.
Children: Paracetamol reduces fever symptoms in children but does not remove the cause or prevent febrile convulsions. Infants and children tolerate low grade fever (eg <38.0–38.5°C) well, and there may be no advantage in giving paracetamol in this situation. Children often respond well to fluids and comfort.
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Safe to use.

**Adverse effects**
Rare with therapeutic doses.
Rare: urticarial or erythematous rash, drug fever and mucosal lesions, neutropenia, thrombocytopenia, pancytopenia, acute hepatitis (single case report), hypotension(IV)
ACUTE OVERDOSE: Single doses >150 mg/kg may result in severe liver damage (which may be fatal), hypoglycaemia and acute renal tubular necrosis. See Gastrointestinal decontaminants, Acetylcysteine.

**Dosage**
Adult, child >12 years
Oral/rectal, 0.5–1 g every 3–6 hours; maximum 4 g daily. For palliative care, doses up to 6 g daily may be used.
Oral controlled release (665 mg), 2 tablets every 6–8 hours swallowed whole. Maximum 6 tablets (3990 mg) daily.
IV infusion, 1 g (100 mL) every 4–6 hours; maximum 4 g daily.
Child
Oral/rectal, 15 mg/kg every 4–6 hours; in an unsupervised, community setting, limit dosage to 60 mg/kg daily for up to 48 hours; up to 90 mg/kg daily can be used under medical supervision with review after 48 hours; single doses of 30 mg/kg may be used for night-time dosing.
IV infusion, 15 mg/kg (1.5 mL/kg) every 6 hours; maximum 60 mg/kg daily.
Combination with codeine
For additional information see Codeine
Adult, 1–2 tablets (of paracetamol 500 mg and codeine 8, 15 or 30 mg) every 3–6 hours if needed, up to a maximum of 8 tablets daily.
Combination with metoclopramide
For additional information see Metoclopramide
Adult, 1–2 tablets (of paracetamol 500 mg and metoclopramide 5 mg) at first warning of migraine; repeat every 4 hours if required.

Administration instructions
Give IV infusion over 15 minutes.

Patient counselling
Do not take more than 8 tablets or capsules (500 mg strength) or 6 controlled release tablets each day. The effect of the controlled release tablets lasts about 8 hours.
Give children paracetamol strictly according to the dose and frequency instructions on the label and if pain and/or fever lasts for >48 hours, talk to your doctor.
There are many brands of paracetamol. It is also contained in many cough and cold products. Prevent overdosing by checking carefully which strength preparation is being used, and the correct dose for that preparation. Avoid using more than 1 product containing paracetamol at the same time. Too much paracetamol can cause liver damage.

Practice points
- paracetamol may be used in all age groups and is preferred to NSAIDs for mild-to-moderate pain as it has fewer adverse effects; it can be used when NSAIDs are contraindicated
- usual maximum dose is 4 g daily; in specialist pain services a higher dose, e.g. 6 g daily, may be used for the first 3–5 days of acute pain
- lack of awareness of the strengths of different paediatric formulations, e.g. infant drops (50 mg/mL or 100 mg/mL) and liquid paracetamol (24 mg/mL or 48 mg/mL), and use of >1 preparation containing paracetamol, may lead to dosage errors and toxicity; educate parents and caregivers appropriately
- onset of pain relief is 5–10 minutes after starting IV infusion, and approximately 30 minutes after oral administration
- rectal absorption can be erratic and delayed; oral administration is preferred
- in osteoarthritis of all grades, paracetamol alone is preferred but under-used
- it is also used with NSAID treatment for all painful conditions, although the evidence is sparse for the superiori of this combination compared with NSAID alone.

Products
PARACETAMOL SUPP. 125 MG (ADOL®, ANTAMOL®, PAMOL®, PYROLITE®, REVANIN®)
PARACETAMOL SUPP. 250 MG (ADOL®, ANTAMOL®, DOLOMOL®, PAMOL®, PYROLITE®, REVANIN®)
PARACETAMOL SUSP. 125 MG/5ML 100 ML BOTTLE (ANTAMOL®, REVANIN®, PAMOL®)
PARACETAMOL TABS 500 MG (ADOL®, ANTAMOL®, CENDOL®, DOLOCET®, DOLOMOL®, JOPAMOL®, PAMOL®, PANADOL®, PANDA®, PARACETAMOL®, PYROLITE®, RAZIMOL®, REMEDOL®, REVANIN®)
PARACETAMOL VIAL 1 GM (AS HCL) 100 ML VIAL (PERFALGAN®)
PARACETAMOL+CAFFEIN+ACETYLSALISALIC ACID TABS 250+65+25 MG (CAFIMOL®, EXCEDRIN®, PANDARIN®)
PARACETAMOL+CODEINE PHOSPHATE TABS 500+10 MG (NORACOD®, REVACOD®)
PARACETAMOL+ORPHENADRIN CITRATE TABS 450+35 MG (MUSCADOL®, MYOGESIC®, NORGESIC®)

04.07.02 Opiod analgesics
CODEINE

Mode of action
Opioid analgesics mimic endogenous opioids by activating opioid receptors in the central and peripheral nervous systems to produce analgesia, respiratory depression, sedation and constipation. They prevent transmission of the pain impulse by acting pre- and post-synaptically in the spinal cord, and by modulating the descending inhibitory pathways from the brain. Cough suppression occurs in the medullary centre of the brain.

The affinity of individual opioid analgesics for receptors varies and opioids may act as pure agonists or partial agonists. Partial agonists demonstrate a 'ceiling response' above which an increase in dose does not produce an additional increase in effect.

Indications
Mild-to-moderate pain (includes combination with aspirin, ibuprofen and paracetamol)
Cough suppression (see Cough suppressants)
Diarrhoea (see Antidiarrhoeals)

Contraindications
Significant respiratory disease (except respiratory indications above).
Comatose patients, unless near death.
Phaeochromocytoma (risk of pressor response due to histamine release which occurs with morphine and some other opioids); however, fentanyl or its derivatives may be used since they do not cause release of histamine.

Specific considerations
Uncorrected endocrine abnormalities, hypothyroidism, adrenocortical insufficiency, acute alcoholism, myasthenia gravis: careful titration of dose of opioids required.
Epilepsy or a recognised risk for seizure, eg head injury, metabolic disorders, alcohol and drug withdrawal, CNS infections: increased risk of seizure.

Untreated raised intracranial pressure: may be used for associated pain in palliative care; seek specialist advice.
Asthma during acute attack, unless ventilated: opioids depress respiration and cough reflex and dry secretions.

Hypotension, shock: reduced blood volume increases hypotensive risk; also impairs IM/SC absorption; careful titration of opioid dose required.
Biliary colic or surgery: all opioids, including pethidine and morphine, may cause spasm of sphincter of Oddi; there appears to be little difference in effect between the different opioids.
Renal impairment: In severe impairment active metabolites accumulate. Give the usual dose but extend the interval between doses, considering patient age and clinical status.

Hepatic impairment: Liver disease does not preclude use of opioids but dose adjustment may be required.
Elderly: Opioid dose requirement decreases progressively with age. In the elderly, use a lower initial dose and titrate to effect. There is an increased risk of adverse effects including cognitive impairment and falls.
Children: Opioid use in children is usually initiated or recommended by specialists.
Neonates and infants up to approximately 12 months are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.
Pregnancy: Safe to use; prolonged high doses of codeine before delivery may produce withdrawal symptoms in the newborn; ADEC category A.
Breastfeeding: Safe to use.

Adverse effects
Type and severity of adverse effects depend on dosage and circumstances of use, eg acute or chronic pain, during anaesthesia.
Repeated use may cause physical and rarely, psychological dependence. Withdrawal symptoms (eg nausea, vomiting, diarrhoea, sweating, anxiety) may occur if chronic treatment is stopped suddenly; prevent by gradually reducing dose before stopping opioid.

Adverse effects may limit achieving adequate pain control. Options for management include:
- controlling symptoms
- reducing the dose of opioid (and possibly adding non-opioid or adjuvant analgesic)
- switching to an alternative opioid ('opioid rotation').
Common: nausea and vomiting, dyspepsia, drowsiness, dizziness, headache, orthostatic hypotension, itch, dry mouth, miosis, urinary retention, constipation
Infrequent: dose-related respiratory depression, bronchospasm, confusion, hallucinations, delirium, agitation, mood changes, tremor, visual disturbances, urticaria, hypothermia, bradycardia or tachycardia, hypertension, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses in palliative care), flushing due to histamine release
(except alfentanil, fentanyl and remifentanil)
Rare: SIADH, anaphylaxis, seizure

**Respiratory depression**
The most serious adverse effect of opioids; this is best judged by the degree of sedation; respiratory rate reduction is a late and unreliable indicator. Sedation is best monitored by using a sedation score, an example of which is given below:

**Sedation score:**
- 0 none
- 1 mild, occasionally drowsy, easy to rouse
- 2 moderate, constantly drowsy (e.g. falls asleep while talking), easy to rouse
- 3 severe, somnolent, difficult to rouse

Sleep: Aim to keep the sedation score <2; a score of 2 represents early respiratory depression.

Nausea and vomiting: May occur initially; an antiemetic may be given prophylactically, but review use within a few days as nausea often lessens with continued opioid use.

Constipation: Occurs with chronic use; tolerance to this develops slowly, if at all. Attention to fluid intake, diet and mobility plus regular laxative use (e.g. senna, sorbitol) is essential as soon as opioids are started; there is no evidence to show that one type of laxative is superior to another.

Cognitive function: Effects on cognitive and psychomotor function are less clear, but are thought to be minimal for most patients receiving stable opioid doses chronically.

**Patient counselling**
This medication may make you feel drowsy and may increase the effects of alcohol. If you are affected, do not drive or operate machinery.

Be careful when you stand up as this medicine might make you feel dizzy if you stand up too quickly.

**Practice points**
- do not use IV route (risk of arrhythmias)
- codeine may be used for moderate pain not controlled by non-opioid analgesics; it is frequently used with paracetamol or aspirin
- 6–10% of Caucasians and 1–2% of Asians lack the enzyme CYP2D6 (necessary for metabolism of codeine to morphine); these people are therefore unlikely to obtain analgesia with codeine
- beware of potential misuse as a street drug

**Combination preparations**
- combinations of codeine 60 mg and paracetamol 1000 mg are more effective for acute pain than paracetamol 1000 mg alone, although the incidence of drowsiness and dizziness is increased
- there is no evidence that combination analgesics containing lower doses of codeine with paracetamol, aspirin or ibuprofen have any benefits over these non-opioids alone

**Dosage**
**Adult:** Oral/SC/IM 30–60 mg every 4 hours; maximum 240 mg in 24 hours. Consider alternative opioid if this dose is reached.
**Child:** SC/IM 0.5 mg/kg/dose every 4–6 hours when required; oral 0.5–1 mg/kg/dose every 4–6 hours but monitor for respiratory depression. Usually initiated or recommended by specialists.

**Practice points**
- do not use IV route (risk of arrhythmias)
- codeine may be used for moderate pain not controlled by non-opioid analgesics; it is frequently used with paracetamol or aspirin
- 6–10% of Caucasians and 1–2% of Asians lack the enzyme CYP2D6 (necessary for metabolism of codeine to morphine); these people are therefore unlikely to obtain analgesia with codeine
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**Combination preparations**
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- there is no evidence that combination analgesics containing lower doses of codeine with paracetamol, aspirin or ibuprofen have any benefits over these non-opioids alone

**Products**
**CODEINE TABS 30 MG (NOT REGISTERED)**
MORPHINE

Mode of action
See codeine.

Indications
Marketed: Moderate-to-severe acute or chronic pain, Opioid adjunct during general anaesthesia
Accepted: Acute pulmonary oedema, adjunct, Relief of severe dyspnoea, eg lung cancer (seek specialist advice)

Contraindications
See codeine.

Specific considerations
Uncorrected endocrine abnormalities, hypothyroidism, adrenocortical insufficiency, acute alcoholism, myasthenia gravis: careful titration of dose of opioids required.

Epilepsy or a recognised risk for seizure, e.g. head injury, metabolic disorders, alcohol and drug withdrawal, CNS infections: increased risk of seizure.

Untreated raised intracranial pressure: may be used for associated pain in palliative care; seek specialist advice.

Asthma during acute attack, unless ventilated—opioids depress respiration and cough reflex and dry secretions.

Hypotension, shock: reduced blood volume increases hypotensive risk; also impairs IM/SC absorption; careful titration of opioid dose required.

Renal impairment: Morphine's active metabolites have a longer half-life than morphine and accumulate in the elderly and in renal impairment; may cause respiratory depression and delirium. Moderate, chronic use requires lower doses; take into account adverse effects and need for adequate analgesia. Severe, reduce dose; avoid chronic use due to accumulation of active metabolites.

Hepatic impairment: Severe, avoid use; may cause excessive sedation or coma.

Biliary colic or surgery—all opioids, including pethidine and morphine, may cause spasm of sphincter of Oddi; there appears to be little difference in effect between the different opioids.

Elderly: Opioid dose requirement decreases progressively with age. In the elderly, use a lower initial dose and titrate to effect. There is an increased risk of adverse effects including cognitive impairment and falls.

Children: Opioid use in children is usually initiated or recommended by specialists.

Neonates and infants up to approximately 12 months are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.

Pregnancy: Opioid analgesics may cause respiratory depression in the newborn; withdrawal effects may occur in neonates of dependent mothers; ADEC category C. Codeine is category A, but prolonged use near term by mother may also produce respiratory and/or withdrawal effects in the newborn.

Breastfeeding: Safe to use.

Adverse effects
See codeine.

Dosage
Titrate dose to patient needs. In acute pain and palliative care there is no maximum dose; only adverse effects limit the morphine dose. In chronic non-cancer pain, involve a specialist pain team in assessing and managing the patient.

The following are approximate dose ranges for patients starting on opioids. Doses will vary widely depending on the indication, e.g. acute or chronic pain, and previous analgesic requirements.

Monitor cardiorespiratory status of patient closely, particularly with continuous infusion or repeated parenteral doses in opioid-naive individuals.

Acute pain, adult
IV, initial dose
0.5–2 mg repeated every 3–5 minutes. This interval may not represent the true time to peak effect (which may be up to 15 minutes). Titrate dose according to response, respiratory rate and sedation score. Use the lower dose in patients >70 years of age.

SC/IM
Suggested doses are for opioid-naive patients and may vary according to the clinical situation; start at lower end of dose range; titrate subsequent doses to the individual’s need.

20–39 years, 7.5–12.5 mg every 2 hours as required.
40–59 years, 5–10 mg every 2 hours as required.
60–69 years, 2.5–7.5 mg every 2 hours as required.
70–85 years, 2.5–5 mg every 2 hours as required.
>85 years, 2–3 mg every 2 hours as required.

Acute pain, child
Neonate: IV infusion, 10–20 micrograms/kg/hour.
Infant, child: IV, 50–100 micrograms/kg/dose every 4 hours. IV infusion, 10–40 micrograms/kg/hour.

**Chronic cancer pain, adult**

**Initial dosing**

Initial dose depends on previous opioid exposure:
- if opioid-naïve, start with 2.5–5 mg oral liquid every 4 hours
- if previously on opioids, consider equianalgesic dose of morphine (see Table 04-6 Opioid comparative information).

Oral liquid, 2.5–20 mg every 4 hours. Initial dose will depend on previous analgesia. Titrate doses to effect and calculate 24-hour morphine requirement.

**Maintenance dosing**

Convert the 24-hour dose of oral liquid into an equivalent dose of a controlled release product for maintenance treatment.

Oral controlled release tablet or controlled release liquid, total daily dose as determined for oral liquid, but give half total daily dose every 12 hours.

Oral controlled release capsule, total daily dose as determined for oral liquid; half total daily dose may be given every 12 hours or total daily dose every 24 hours; total daily dose every 24 hours.

SC infusion, calculate 24-hour oral dose of morphine and give one-third by SC infusion over 24 hours.

**Chronic non-cancer pain, adult**

Involve a specialist pain team in managing these patients. Start with the equivalent of controlled release morphine 5–30 mg twice daily and adjust dose according to the response after 1 week or less. Use regular (by the clock) dosing. In general, avoid short acting preparations.

**Breakthrough pain**

Use additional doses of morphine liquid for breakthrough pain, using one-twelfth to one-sixth of the daily requirement given as frequently as required. If repeated breakthrough doses are required, adjust the regular baseline morphine dose.

Chronic cancer pain, infant and child: SC infusion, 30–60 micrograms/kg/hour.

Acute pulmonary oedema: IV, 1–5 mg. Use lower end of dose range in the elderly.

Renal impairment: Moderate impairment, give three-quarters of estimated required dose. Severe impairment, give half of estimated dose and watch for excessive sedation; avoid chronic use.

**Dose equivalence**

For chronic dosing, 30 mg oral morphine is equivalent to 10 mg SC/IM/IV morphine.

Use the same dose for sulfate, tartrate and hydrochloride salts.

For equivalent doses of other opioids, see Table 04-6 Opioid comparative information.

**Administration instructions**

For IV use, dilute and give over 4–5 minutes.

Compatible fluids: sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%.

Controlled release capsules may be opened, the pellets mixed with 10–20 mL of water or liquid feed, and given through a 16 or 20 gauge French gastrostomy tube, then rinsed through with more liquid to ensure all pellets are used. Do not crush pellets.

**Patient counselling**

Controlled release tablets must be swallowed whole; do not crush or chew them.

Controlled release capsules may be opened, and the pellets sprinkled on soft food or mixed with 30 mL liquid. Take within 30 - 60 minutes. Do not crush or chew pellets.

For controlled release suspension, add the contents of the sachet to the recommended amount of water, mix thoroughly and take immediately.

This medication may make you feel drowsy and may increase the effects of alcohol. If you are affected, do not drive or operate machinery.

Be careful when you stand up as this medicine might make you feel dizzy if you stand up too quickly.

**Practice points**

- peak analgesia following a dose of morphine occurs:
  - within 60 minutes after conventional oral liquid
  - 30–60 minutes after SC/IM
  - 10–15 minutes after IV
  - 4–5 hours after MS Contin® or MS Mono®
  - 8–15 hours after Kapanol®
• do not use controlled release preparations for acute pain management as slow onset and offset make rapid, safe titration impossible
• reassess the patient's pain frequently and adjust dose of morphine accordingly
• if morphine overdose occurs in severe renal impairment, infusion of naloxone for several days may be necessary
• morphine is the preferred opioid analgesic for moderate-to-severe pain because of familiarity, availability and cost (rather than superior efficacy); other opioids may be used where adverse effects of morphine are unacceptable
• a key advantage of opioids in the management of pain is that they can be given by a variety of routes (oral, transmucosal, rectal, IV, SC, IM, transdermal, epidural and intrathecal); they can also be easily titrated, are highly effective and have a favourable risk/benefit ratio
• always use a stimulant laxative (eg docusate with senna) unless contraindicated, or an osmotic laxative (eg sorbitol), for people requiring regular opioids, see Laxatives
• do not crush controlled release preparations as this results in more rapid and unpredictable absorption
• sufentanil (available through the SAS), remifentanil and alfentanil are shorter acting derivatives of fentanyl used for analgesia during anaesthesia; SC sufentanil has been used as an alternative to SC fentanyl for palliative care as a smaller volume of infusion is required
• naloxone is used to reverse opioid sedation and respiratory depression

Dosage considerations
• higher doses of opioids may be required to achieve adequate analgesia in patients on chronic opioid treatment or with a history of opioid misuse
• titrate dose to effect using small increments as dose required may vary more than 10-fold between patients of similar age, irrespective of weight
• assess pain intensity, cardiorespiratory status, level of sedation and other adverse effects frequently to guide ongoing treatment, particularly with continuous infusion or repeated parental doses in opioid-naïve individuals and in the elderly, see Adverse effects
• high doses and/or rapid IV administration may cause rapid onset respiratory depression, circulatory collapse and even cardiac arrest; titrate to effect with small doses and ensure naloxone and resuscitation equipment are immediately available

Products
MORPHIN TABS 10 MG IMMEDIATE RELEASE (AS SULFATE) (HIKMA MORPHINE®, MST. CONT®)
MORPHIN TABS 30 MG SUSTAINED RELEASE (AS SULFATE) (MST. CONT®)
MORPHIN TABS 60 MG SUSTAINED RELEASE (AS SULFATE) (MST. CONT®)

TRAMADOL
Mode of action
Binds to mu opioid receptors and also inhibits reuptake of noradrenaline and serotonin.

Indications
Moderate-to-severe pain (including neuropathic).

Contraindications
Allergy to tramadol.
Treatment with, or within 14 days of, a MAOI.
Significant respiratory disease (except respiratory indications above).
Comatose patients, unless near death.
Phaeochromocytoma.

Specific considerations
Treatment with drugs which can contribute to the serotonin syndrome: may increase likelihood of serotonin syndrome; avoid combinations or monitor clinical course carefully.
Uncorrected endocrine abnormalities, hypothyroidism, adrenocortical insufficiency, acute alcoholism, myasthenia gravis: careful titration of dose of opioids required.
Epilepsy or a recognised risk for seizure, e.g. head injury, metabolic disorders, alcohol and drug withdrawal, CNS infections: increased risk of seizure.
Untreated raised intracranial pressure: may be used for associated pain in palliative care; seek specialist advice.
Asthma during acute attack, unless ventilated: opioids depress respiration and cough reflex and dry secretions.
Hypotension, shock: reduced blood volume increases hypotensive risk; also impairs IM/SC absorption; careful titration of opioid dose required.
Biliary colic or surgery: all opioids, including pethidine and morphine, may cause spasm of sphincter of Oddi; there appears to be little difference in effect between the different opioids.

Renal impairment: Decreased rate of excretion of tramadol and its active metabolite. Reduce dose in moderate-to-severe impairment. Avoid use in severe impairment.

Hepatic impairment: Reduce dose in cirrhosis. The controlled release formulation should not be used in patients with severe hepatic insufficiency.

Elderly: Do not exceed 300 mg daily in people >75 years.

Children: Used by specialist paediatricians, but manufacturer does not recommend use in children.

Adjust dose or use an alternative opioid, such as fentanyl or oxycodone.

Hepatic impairment: Liver disease does not preclude use of opioids but dose adjustment may be required.

Reduce dose and titrate carefully in severe hepatic disease as may precipitate coma.

Elderly: Opioid dose requirement decreases progressively with age. In the elderly, use a lower initial dose and titrate to effect. There is an increased risk of adverse effects including cognitive impairment and falls.

Children: Opioid use in children is usually initiated or recommended by specialists.

Neonates and infants up to about 12 months of age are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.

Pregnancy: Opioid analgesics may cause respiratory depression in the newborn; withdrawal effects may occur in neonates of dependent mothers; ADEC category C. Codeine is category A, but prolonged use near term by mother may also produce respiratory and/or withdrawal effects in the newborn.

Lactation: Safe to use.

Adverse effects

Common: headache, CNS stimulation, weakness, sweating, sleep disorder, dyspepsia, itch, rash.

Infrequent: depression, difficulty concentrating.

Rare: anaphylactoid reactions, Stevens–Johnson syndrome, toxic epidermal necrolysis, seizure, coordination disturbance.

Dosage

IV/IM, 50–100 mg every 4–6 hours, up to a total daily dose of 600 mg.

Oral, conventional formulation, 50–100 mg every 4–6 hours when necessary; maximum 400 mg daily.

Oral, controlled release formulation, 100–200 mg every 12 hours. Maximum 400 mg daily. Do not use controlled release formulation for initial stabilisation.

Patient-controlled analgesia, see hospital protocols.

Moderate renal impairment

IM/oral (conventional formulation), 50–100 mg every 12 hours.

Oral (controlled release formulation), 100–200 mg every 24 hours.

Hepatic impairment

Cirrhosis, (conventional formulation) 50 mg every 12 hours.

Patient counselling

Controlled release tablets, swallow whole; do not crush or chew them.

Oral liquid, if you have not used the dosage pump for more than 7 days, press the nozzle 5 times before use to ensure you get the correct dose.

This medication may make you feel drowsy and may increase the effects of alcohol. If you are affected, do not drive or operate machinery.

Be careful when you stand up as this medicine might make you feel dizzy if you stand up too quickly.

Practice points

• analgesia starts within 1 hour and peaks at 2–4 hours

• effective for moderate pain and also useful in neuropathic pain; risk of constipation is less than with other opioids

• IV bolus doses >50 mg are associated with increased incidence of nausea and vomiting

• do not use controlled release preparations for acute pain management as slow onset and offset make rapid, safe titration impossible

• for postoperative pain, a single oral dose of 100 mg tramadol has similar efficacy but greater incidence of adverse effects than paracetamol 650 mg with dextropropoxyphene 65 mg

• for moderate postoperative pain, IM/IV tramadol is as effective as morphine but for severe acute pain it is less effective

• may be used for patients who have excessive respiratory depression, sedation, hypoxaemia or constipation with other opioids and whose pain is poorly controlled following reduction of opioid dose
hospital protocols for use in adults may differ from the manufacturer's dosing schedules

- tramadol has relatively weak affinity for opioid receptors and its misuse potential appears to be low; it is designated as a Schedule 4 product and not a controlled substance
- there is little evidence that tramadol causes seizures although they have been reported after its use; as with all opioids, use caution in patients with epilepsy or a recognised risk of seizure
- naloxone only partially antagonises tramadol overdose, and may increase the risk of seizures.

**Products**

- **TRAMADOL AMPS 100 MG/AMP (AS HCL) 2 ML AMP (MABRON®, TRAMADON®, TRAMAL®)**
- **TRAMADOL CAPS 50 MG (ANALDOL®, MABRON®, NOMAL®, PAINOL®, TAROL®, TRAMADON®, TRAMAL®)**

**04.07.03 Opioid dependence**

**METHADONE**

**Mode of action**
See codeine.

**Indications**
Severe chronic pain
Management of opioid dependence

**Contraindications**
Significant respiratory disease (except respiratory indications above)
Comatose patients, unless near death
Phaeochromocytoma (risk of pressor response due to histamine release which occurs with morphine and some other opioids); however, fentanyl or its derivatives may be used since they do not cause release of histamine.

**Specific considerations**
Risk factors for prolonged QT interval: in high doses, methadone may further prolong the QT interval and increase risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
Uncorrected endocrine abnormalities, hypothyroidism, adrenocortical insufficiency, acute alcoholism, myasthenia gravis: careful titration of dose of opioids required.
Epilepsy or a recognised risk for seizure, eg head injury, metabolic disorders, alcohol and drug withdrawal, CNS infection: — increased risk of seizure.
Untreated raised intracranial pressure: may be used for associated pain in palliative care; seek specialist advice.
Asthma during acute attack, unless ventilated: opioids depress respiration and cough reflex and dry secretions.
Hypotension, shock: reduced blood volume increases hypotensive risk; also impairs IM/SC absorption; careful titration of opioid dose required.
Biliary colic or surgery: all opioids, including pethidine and morphine, may cause spasm of sphincter of Oddi; there appears to be little difference in effect between the different opioids.
Renal impairment: Reduced dose may be required in severe impairment.
Hepatic impairment: Liver disease does not preclude use of opioids but dose adjustment may be required. Reduce dose and titrate carefully in severe hepatic disease as may precipitate coma.
Elderly: Opioid dose requirement decreases progressively with age. In the elderly, use a lower initial dose and titrate to effect. There is an increased risk of adverse effects including cognitive impairment and falls.
Children: Opioid use in children is usually initiated or recommended by specialists.
Neonates and infants up to approximately 12 months are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.
Pregnancy: Increased doses (or twice daily administration) may be required due to increased metabolism; ADEC category C.
Breastfeeding: Safe to use.

**Adverse effects**
Infrequent: pain and swelling may occur at injection site
Rare: impotence; prolonged QT interval, torsades de pointes (with high doses)
Other adverse effects: Same as codeine

**Dosage**
Severe chronic pain, opioid-naïve, young adult, oral, 5–10 mg every 6–8 hours initially. Dose titration must be very cautious in view of its long elimination half-life. It may take up to 2 weeks to see adverse effects. In chronic use, manufacturer recommends no more than twice daily dosing.
Cancer pain, see Dose equivalence.
Severe renal impairment
Give half to three-quarters of dose at increased intervals.
Dose equivalence
Based on single dose studies, 20 mg oral methadone is approximately equianalgesic to 10 mg SC/IM methadone.
Dose equivalence for chronic analgesia—ratio of oral morphine:oral methadone during chronic use is approximately 10:1. Use caution in changing patients from morphine to methadone as there is considerable variation in dose equivalence between patients. The equianalgesic dose varies depending on the prior opioid dose. Discuss the conversion with a chronic pain or palliative care specialist.

Patient counselling
This medication may make you feel drowsy and may increase the effects of alcohol. If you are affected, do not drive or operate machinery.

Practice points
- not suitable for acute pain management as the long half-life makes rapid, safe titration difficult
- if daily doses >30 mg are needed for chronic pain consult a pain management clinic
- methadone has high oral bioavailability, but a long and variable duration of effect in chronic use makes dose adjustment difficult
- long duration of effect is useful in treating opioid dependence

Products
METHADONE ORAL SOLUTION 0.1 % (AS HCL) 500 ML BOTTLE (METHADONE®)

Morphine is the preferred opioid analgesic for moderate-to-severe pain because of familiarity, availability and cost (rather than superior efficacy); other opioids may be used where adverse effects of morphine are unacceptable.

A key advantage of opioids in the management of pain is that they can be given by a variety of routes (oral, transmucosal, rectal, IV, SC, transdermal, epidural and spinal); they can also be easily titrated, are highly effective and have a favourable risk/benefit ratio.

Always use a stimulant laxative (e.g. docusate with senna) unless contraindicated, or an osmotic laxative (e.g. sorbitol), for people requiring regular opioids.

Do not crush controlled release preparations as this results in more rapid and unpredictable absorption.

Sufentanil (available through the SAS), remifentanil and alfentanil are shorter acting derivatives of fentanyl used for analgesia during anaesthesia; SC sufentanil has been used as an alternative to SC fentanyl for palliative care as a smaller volume of infusion is required.

Naloxone is used to reverse opioid sedation and respiratory depression.

Dosage considerations
Higher doses of opioids may be required to achieve adequate analgesia in patients on chronic opioid treatment or with a history of opioid misuse.

Titrated dose to effect using small increments as dose required may vary more than 10-fold between patients of similar age, irrespective of weight.

Assess pain intensity, cardiorespiratory status, level of sedation and other adverse effects frequently to guide ongoing treatment, particularly with continuous infusion or repeated parenteral doses in opioid-naive individuals and in the elderly.

High doses and/or rapid IV administration may cause rapid onset respiratory depression, circulatory collapse and even cardiac arrest; titrate to effect with small doses and ensure naloxone and resuscitation equipment are immediately available.

04.07.04 Antimigrane drugs

MIGRAINE
Rationale for drug use
Relief of headache and associated symptoms. Prevention of recurrent migraine.

Before starting treatment
Exclude other causes of headache, particularly in the presence of abnormal neurological examination, new onset in middle age, or a substantial change in headache pattern.

Drugs can cause headache: as an adverse effect, following withdrawal, or secondary to overuse Consider the possibility that >1 type of headache may be involved.

Acute migraine
Non-drug treatment: Rest or sleep in a dark and quiet room; relaxation techniques may be of benefit.
First line drug treatment for mild-to-moderate migraine is usually an analgesic such as paracetamol or NSAID. If these are consistently ineffective (e.g. over 3 attacks) or if migraine is severe, use a migraine-specific agent (5HT1 agonist, ergot alkaloid) at the onset of the attack. Alternative migraine-specific drugs may be tried over subsequent episodes to identify the most effective agent for a particular patient. Consider adding an antiemetics for nausea and vomiting and for those who do not respond to an analgesic alone.

**Analgesics**

There have been few studies of the effectiveness of analgesics in migraine, but NSAIDs, e.g. ibuprofen, naproxen, are known to be beneficial in practice; paracetamol alone may be less effective. Ensure analgesics are taken in sufficient dosage and early in the attack, before nausea and reduced GI motility slow absorption and reduce efficacy; use soluble preparations in preference. Avoid opioids (including combinations of paracetamol or aspirin with codeine or dextropropoxyphene) because they aggravate GI symptoms, have a risk of dependence, and there is little evidence for their effectiveness in acute migraine.

**Antiemetics**

Antiemetics alone may be effective in relieving the headache of migraine, and when combined with other treatments for migraine, they may have an additional analgesic effect. Metoclopramide or domperidone may be used orally at the onset of symptoms and then every 6–8 hours if needed. They reduce nausea and vomiting, increase GI motility and improve absorption of analgesics. When nausea or vomiting are prominent, metoclopramide (IM/IV) or prochlorperazine (IM/IV or rectally) may be used. There is a risk of EPSE (e.g. acute dystonic reaction, especially in children and young adults) with metoclopramide and prochlorperazine.

**5HT1 agonists (triptans)**

5HT1 agonists relieve headache in 50–75% of people approximately 2–4 hours after oral administration. They also improve associated symptoms such as nausea, vomiting, photophobia and phonophobia. About one-third of patients may have recurrence of headache, which may be relieved with a second dose. All are effective, well tolerated and safe. However, the response to each agent can vary considerably between patients. Triptans are most effective if taken when the headache is beginning to develop, and not earlier (e.g. during aura) or later (when headache more severe). Sumatriptan is the most studied; there are limited data comparing sumatriptan to naratriptan and zolmitriptan. Few trials directly compare 5HT1 agonists to analgesics or ergot alkaloids. Efficacy of sumatriptan is similar to diclofenac or aspirin with metoclopramide, and greater than ergotamine with caffeine.

**Ergot alkaloids**

Use of ergot alkaloids is limited by adverse effects (e.g. peripheral vasoconstriction) and lack of evidence regarding effective doses; also associated with high risk of overuse syndromes and rebound headaches. Ergotamine can be used orally or rectally; dihydroergotamine is better given SC or IM because of poor oral bioavailability. They should be taken at the onset of a migraine attack. Do not use with 5HT1 agonists.

**Prevention of migraine**

Non-drug treatment: Self management is the key. Identify and manage trigger factors if possible, e.g. specific foods, stress, irregular sleep habits, bright lights, overwork. Often there is no obvious cause. Relaxation and behavioural therapy may be beneficial, but more evidence is required for the effectiveness of techniques such as acupuncture and spinal manipulation.

**Drug choice**

Consider regular preventive drug treatment if the person has 2 or 3 severe migraine attacks each month which significantly impair quality of life and do not respond well to treatment taken at the start of attacks. Take patient preference into account, as compliance with these drugs is often low. Prophylactic drugs are relatively non-specific, their efficacy is moderate at best, and they are associated with significant adverse effects. Many are not approved for this indication. First line drugs are beta-blockers and amitriptyline; valproate is second line. Other drugs are used but either evidence for their efficacy is limited (e.g. topiramate, gabapentin) or they have serious adverse effects (e.g. methysergide, pizotifen). The choice of treatment involves balancing clinical response and tolerability as well as considering coexisting diseases for which the drug may also be of benefit (e.g. beta-blockers for migraine and angina or hypertension). Treatment for acute attacks will still be required as preventive therapy only reduces frequency and severity of attacks; also it may take 1–3 months for the full effect of the preventive drug to be seen. Use only 1 preventive agent at a time. Start at a low dose and increase gradually up to the lowest effective dose. If
the drug is effective, continue treatment for 4–6 months and then, to establish if it is still required, gradually withdraw over 2–3 weeks (rebound headaches may occur with rapid withdrawal). Long term prophylaxis may be necessary in some patients, but evidence of benefit is weak.

Beta-blockers with no intrinsic sympathomimetic activity can be effective in decreasing the frequency of migraine attacks.

Propranolol is the most studied, and there is definite evidence of its efficacy for this indication. Metoprolol is also approved for migraine prevention and atenolol, while not specifically approved, is frequently used. Although evidence is more limited, both are effective in preventing migraine.

Therapeutic failure with one beta-blocker does not predict response to another, so consecutive trials of different drugs may be appropriate.

Amitriptyline: Although not marketed for this indication, amitriptyline has been shown to be effective (evidence is lacking regarding the efficacy of other TCAs). It may be particularly useful in patients with associated tension headache. Start with a low dosage at bedtime, and gradually increase.

Valproate: There is consistent evidence for the effectiveness of valproate in reducing migraine frequency even though it is not approved for this indication.

Its use in women of child-bearing potential is limited by the risk of congenital malformation.

Methysergide is considered to be the best prophylactic agent, but its use is limited by a high incidence of adverse effects. Reserve its use for prevention of severe recurrent migraine attacks or cluster headache unresponsive to other treatments.

Other drugs
Topiramate: marketed for migraine prophylaxis. Limited studies suggest that it is more effective than placebo, and possibly as effective as propranolol, in reducing frequency of migraine.
Gabapentin: may have modest efficacy, but evidence is limited.
Pizotifen: may be effective, but is poorly tolerated with a high rate of withdrawal due to adverse effects, particularly drowsiness and weight gain.
Cyproheptadine and clonidine: although still marketed for prevention of migraine, these drugs are used rarely now and evidence for their efficacy is lacking.

Special cases
Cluster headache: Cluster headache is a rare but debilitating form of headache. Each attack is short-lived but multiple attacks may occur each day. Prevention is the mainstay of treatment; abortive agents are used for breakthrough headache.
Prevention: Start treatment at the first sign of an attack and continue for 2 weeks after the last attack before tapering dosage gradually and stopping until the next attack. Several drugs, e.g. verapamil, methysergide and pizotifen, may be effective but more research is needed.

Breakthrough treatment: Inhaling oxygen (7 L/minute for 10 minutes) at the onset of symptoms may relieve pain in about 70% of people within 15 minutes. SC sumatriptan is similarly effective.

Sumatriptan nasal spray is also used and may improve or abolish headache within 30 minutes.

Ergotamine and dihydroergotamine are marketed for use in acute attacks but evidence for their efficacy is lacking.

Methysergide is triggered by reduction in oestrogen and occurs exclusively within 1–2 days of the start of a period. Migraine occurring at other times of the menstrual cycle is termed menstrual-associated migraine.

Acute treatment is the same as for other types of migraine. Prevention includes taking an NSAID for the duration of the period and/or use of oestrogen supplements for 7 days, starting 3 days before menstruation.

Children: Management is similar to that in adults but fewer drugs are approved for treatment of migraine in children.

Acute attacks
Paracetamol or NSAID (avoid aspirin in children <18 years) are usually effective; nasal sumatriptan appears to relieve migraine in adolescents aged 12–17 years. Although antiemetics (e.g. prochlorperazine, promethazine) may be used to reduce nausea and vomiting, evidence regarding their efficacy in paediatric migraine is lacking.

Behavioural therapy, particularly biofeedback with or without progressive muscle relaxation, may be useful.

Prevention
Evidence for efficacy in prevention of migraine in children is conflicting for propranolol, and insufficient for drugs such as amitriptyline, topiramate and valproate. Pizotifen is ineffective.

Medication overuse headache
Associated with all drugs (including paracetamol and NSAIDs) used for treating acute migraine and can occur in adults and children. Risk increases with regular use of medication on >2 days/week.

Diagnosis is more likely with headache occurring on >15 days/month and regular use of:

- Paracetamol and/or NSAIDs on >14 days/month for >3 months or
• Migraine-specific drugs, opioids or combination analgesics on >9 days/month for >3 months.

**Management**
Treatment involves withdrawing the overused drugs (which may require specialist referral). Withdrawal symptoms last 2–10 days, but complete resolution may take months and relapse is common. Reduce necessity for acute treatment by using adequate preventive therapy to manage frequent headaches.

**Practice points**
- Ask the patient to keep a diary recording drugs and dosages used, and response to treatment, including adverse effects
- In addition to medication overuse headache, overuse of 5HT1 agonists, ergot alkaloids or opioids (including combinations of paracetamol or aspirin with codeine or dextropropoxyphene) may be associated with dependence and subsequent withdrawal syndrome
- Migraine is associated with an increased risk of depressive and anxiety disorders, which may require treatment
- There is little evidence for combining analgesics or antiemetics with 5HT1 agonists, but consider this if 5HT1 agonist alone is ineffective.

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**04.07.04.01 5HT1 agonists (TRIPTANS)**

**ELETREPTAN**

**Mode of action**
Constrict cranial vessels by acting selectively at 5HT1B/1D receptors, also thought to inhibit the abnormal activation of the trigeminal nociceptors.

**Indications**
Acute relief of migraine in people >12 years.

**Contraindications**
As for Sumatriptan, Eletriptan should not be given with potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as erythromycin and ketoconazole; increased plasma levels of eletriptan have been noted after such combinations.

**Specific considerations**
- Breast feeding: Eletriptan is distributed into human breast milk and the manufacturer has suggested that infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.
- Hepatic impairment: No dose adjustment for eletriptan is needed in patients with mild to moderate hepatic impairment. Eletriptan has not been studied in patients with severe hepatic impairment and therefore the manufacturers do not recommend its use.
- Renal impairment: A dose of 20 mg of eletriptan is recommended in patients with mild to moderate renal impairment, increased if necessary to 40 mg. The maximum daily dose should not exceed 40 mg. Eletriptan should not be used in severe renal impairment.

**Adverse effects**
Common: transient pain at injection site, transient burning sensation in the nose or throat (nasal spray).

**Dosage**
The usual dose is 40 mg; if this is ineffective a second dose should not be taken for the same attack. If the headache recurs within 24 hours a second dose may be taken after an interval of at least 2 hours. Doses of 80 mg may be used in subsequent attacks, but should not be repeated within a 24-hour period.

**Products**
ELETREPTAN TABS 40 MG (AS HCL) (RELPAX®)

**SUMATRIPTAN**

**Mode of action**
Constrict cranial vessels by acting selectively at 5HT1B/1D receptors, also thought to inhibit the abnormal activation of trigeminal nociceptors.

**Indications**
Acute relief of migraine.
Acute relief of cluster headache (injection).
Contraindications
Severe hepatic impairment.
Manufacturer contraindicates use with, or within 14 days of stopping, a MAOI.
Manufacturer contraindicates use with, or within 24 hours of stopping, an ergot alkaloid or methysergide.
History of MI, ischaemic heart disease, coronary vasospasm, eg Prinzmetal’s angina
Uncontrolled hypertension
History of cerebrovascular accident or TIA
Peripheral vascular disease
Specific considerations
Risk factors for ischaemic heart disease: higher risk of cardiovascular adverse effects.
Treatment with drugs which can contribute to the serotonin syndrome, may increase likelihood of serotonin syndrome; avoid combinations or monitor clinical course carefully.
Elderly: Use not recommended.
Pregnancy: Limited data; appear acceptable; ADEC category B3.
Breastfeeding: Avoid use.
Adverse effects
Common: transient pain at injection site, transient burning sensation in the nose or throat (nasal spray).
sensations of tingling, heat, pain, heaviness or tightness in any part of the body including chest and throat, flushing, dizziness, feeling of weakness, drowsiness, fatigue, nausea, vomiting, dry mouth, transient increase in BP
Infrequent: rash
Rare: angina, MI and death, arrhythmias, stroke, seizures, anaphylaxis
Dosage
Use as soon as possible after onset of headache.
Oral, 50–100 mg. Dose may be repeated after at least 2 hours if migraine recurs. Maximum daily dose 300 mg.
SC, 6 mg. Dose may be repeated after at least 1 hour if migraine recurs. Maximum daily dose 12 mg.
Intranasal, 10–20 mg into 1 nostril. Dose may be repeated after at least 2 hours if migraine recurs. Maximum daily dose 40 mg.
Patient counselling
This medication is most effective if taken when the headache is beginning to develop, and not earlier (eg during aura) or later (when headache more severe).
This medicine may make you feel drowsy or dizzy; if you are affected, do not drive or operate machinery.
If there is no improvement with the first dose, do not repeat.
Practice points
• 100 mg oral dose is little better than 50 mg in most people; it has more adverse effects, but can be used if the lower dose is ineffective
• SC administration seems more effective than oral but causes more adverse effects; intranasal administration has a quicker onset of action than oral but has a shorter duration of action
• intranasal, but not oral, sumatriptan is effective in adolescents (12–17 years) in whom migraine attacks are of relatively short duration
Products
SUMATRIPTAN PFS 6 MG/0.5ML (AS SUCCINATE)  0.5 ML SYRINGE (IMIGRAN®)
SUMATRIPTAN TABS 50 MG (AS SUCCINATE) (IMIGRAN®, APIGRANE®)

04.07.04 02 Other antimigrane drugs

Pizotifen
Mode of action
5HT2 antagonist with antihistaminic and weak anticholinergic properties.
Indications
Prevention of recurrent migraine and cluster headache.
Specific considerations
Closed angle glaucoma, prostate hypertrophy—risk of aggravation.
Pregnancy: Limited data available; ADEC category B1.
Breastfeeding: No data available.
Adverse effects
Common: sedation, fatigue, nausea, increased appetite, weight gain
Infrequent: dry mouth, constipation, dizziness
Rare: depression, agitation, anxiety, insomnia, rash, myalgia

**Dosage**
Adult, initially 0.5 mg daily at night, gradually increase to 1.5 mg daily in a single dose at night or in divided doses. Maximum, 3–4.5 mg daily in 2 or 3 divided doses.
Child, initially 0.5 mg daily at night, gradually increase to 1.5 mg daily in divided doses. Maximum single dose at night, 1 mg.

**Patient counselling**
Pizotifen may make you feel drowsy especially when you first start to take it and may increase the effects of alcohol; do not drive or operate machinery if you are affected.
Your appetite may increase when taking this medicine and you may need to pay more attention to your diet to avoid weight gain.

**Practice points**
- increase dosage gradually to avoid drowsiness

**Products**
PIZOTIFEN TABS 0.5 MG (AS MALEATE) (PIZOFEN®, SANDOMIGRAN®)

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**04.08 ANTIEPILEPTICS**

**EPILEPSY**

**Rationale for drug use**
Prevention of seizures and associated complications.
Acute treatment of seizures including status epilepticus and febrile convulsions.

**Before starting treatment**
Exclude non-epileptic causes such as breath-holding attack, arrhythmia, pseudoseizures.
Classify type of epilepsy on basis of description of seizures, neurological examination, EEG findings and neuroimaging.
Identify and avoid precipitants if possible (e.g. drugs, sleep deprivation, alcohol withdrawal).

**When to start treatment**
Start antiepileptic medication when the impact of further seizures outweighs the risks of treatment.

**After first seizure**
After 1 seizure only 30–50% of people will have a recurrence. Factors to consider when deciding to treat include:
- Symptomatology (previous seizures may have been unrecognised, e.g. in complex partial seizures)
- Signs (an abnormal EEG or neurological abnormalities may indicate an increased risk of recurrence)
- Seizure type (certain syndromes are more likely to be recurrent, e.g. juvenile myoclonic epilepsy, partial seizures)
- Age (elderly people are at higher risk of recurrence)
- The person's wishes.

Lowest recurrence rates are associated with a normal EEG and no identifiable cause for seizures or when there is a clear avoidable precipitant.

**After second seizure**
Treatment is usually indicated when 2 or more seizures have occurred within 6–12 months (about 80% of people will have recurrent seizures after 2 seizures), except when there is a clear avoidable precipitant or with some types of seizures (e.g. benign childhood epilepsy with centrotemporal spikes).

**Drug choice**
See also Table 04-07 Choice of antiepileptic drug
Specific diagnosis of seizure type is the most important factor for drug selection.
Carbamazepine is often considered to be the drug of choice for partial seizures.
Valproate is regarded as first line treatment for generalised seizures.
Lamotrigine may be used in adults as monotherapy in partial and generalised seizures and it appears to be as effective as carbamazepine. It is also used as adjunctive treatment. Its use is limited by risk of severe adverse reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis.
Oxcarbazepine (structurally related to carbamazepine), is effective as monotherapy or adjunctive treatment in partial seizures or generalised tonic-clonic seizures. Unlike carbamazepine, it does not autoinduce its metabolism, and it has less interaction potential. It may be an alternative in patients unable to tolerate carbamazepine.
Gabapentin, levetiracetam, pregabalin, tiagabine and topiramate are newer antiepileptic drugs which are mainly used
as adjunctive treatment. Vigabatrin should be used only when all other appropriate drug combinations have failed. It may cause visual field defects in 20–40% of patients. Due to the difficulty of monitoring visual fields in young children, only consider for infantile spasms where there are no safer alternatives. Acetazolamide and sulthiame are approved for epilepsy. However, evidence for their clinical efficacy is limited.

**Treatment regimens**
Start treatment with 1 first line drug only. Increase the dose gradually, especially for carbamazepine and lamotrigine. 70–80% of people will have no seizures after treatment with a first line drug.

**Treatment failure**
Before changing drug treatment, check:
Compliance: with the prescribed regimen; plasma concentration monitoring can be helpful. Noncompliance is a common reason for treatment failure.
Dose: ensure dose of first line drug is maximal with minimal adverse effects.
If treatment still ineffective, add an alternative first line drug. When the optimal dosage of the second drug has been achieved, gradually decrease dosage of the first drug.

**Combination treatment**
Exhaust all reasonable options for monotherapy before considering long term treatment with >1 drug. Try 2 first line drugs together before trying a combination of a second line drug and one of the first line drugs. Reconsider the diagnosis if the person is apparently refractory to treatment.
In people with uncontrolled seizures taking >1 antiepileptic drug, simplifying the regimen may improve seizure control. An effective dose of 1 antiepileptic is better than ineffective doses of 2 or more antiepileptics.

**Treatment withdrawal**
This may be attempted after 2–3 years without seizures. Good prognostic signs for remaining seizure-free at the time of withdrawal are a history of few seizures, presence of only absence seizures, younger age when seizure control achieved, normal neurological examination and absence of brain lesions.
When withdrawing treatment, reduce the dosage of antiepileptic drugs over several weeks to months.

**Other treatment**
Surgery may be considered in people with intractable partial epilepsy.

**Special cases**

**Simple febrile seizures**
Simple febrile seizures (brief, generalised, occurring only once in 24 hours and associated with a fever from a source outside the CNS) occur in about 3% of children between 6 months and 5 years of age. There is a 30–50% risk of recurrent febrile seizures, but a low risk of chronic epilepsy and no documented risk of other adverse outcomes. Acute treatment: use diazepam (IV or rectal) or midazolam (IV, IM, intranasal) for the treatment of prolonged seizures.
Prevention: give diazepam (oral or rectal) at the onset of fever for prevention of frequent recurrent seizures. Long term treatment with phenobarbital or valproate is effective in decreasing recurrent febrile seizures but is rarely justified, given their adverse effects and the usually favourable prognosis; consider for children with prolonged and recurrent seizures.
Epilepsy in women: Women of child-bearing potential. Consider and discuss the possibility of pregnancy before selecting a specific antiepileptic drug. The risks of unplanned treatment withdrawal should also be discussed.

**Contraception**
Several antiepileptic drugs (carbamazepine, phenytoin, oxcarbazepine, barbiturates, topiramate) induce hepatic enzymes and increase the metabolism of many drugs, including oral contraceptives. Use of these antiepileptic drugs is associated with a high risk of oral contraceptive failure which is not necessarily accompanied by breakthrough bleeding. High dose COC (at least 50 micrograms ethinyloestradiol) or medroxyprogesterone depot given every 10 weeks may be used but there is still a risk of contraceptive failure. Non-hormonal contraception such as copper-releasing IUD, is preferable.

**Before pregnancy**
Consider withdrawal of antiepileptic treatment in women planning pregnancy who have been seizure-free for at least 2 years. Stopping drug treatment after the diagnosis of pregnancy may not lower the risk of congenital malformations. The evidence for efficacy of folic acid in reducing risk of spina bifida in children of women taking antiepileptic drugs is limited. However, it is recommended to give folic acid for at least 1 month before, and for 3 months after, conception in these women.

**Pregnancy**
The incidence of congenital malformations in infants of mothers treated with antiepileptic drugs is approximately 2–3 times higher than in the general population (4–6% versus 2–3%). The risk increases with the number of
antiepileptic drugs taken. Facial dysmorphism, orofacial clefts, cardiac defects, and digital and nail dysplasia may occur with several antiepileptic drugs, in particular phenytoin, valproate and carbamazepine. There is also an increased risk of spina bifida with valproate and, to a lesser extent, with carbamazepine.

Changes in pharmacokinetics—plasma concentrations of antiepileptic drugs may fall during pregnancy. Compliance may also be a problem. Monitor clinically and with plasma concentrations if indicated; adjust dosage if necessary. Benzodiazepines and barbiturates—use late in pregnancy is associated with risk of respiratory depression and withdrawal symptoms in the infant. Benzodiazepines may also cause neonatal hypotonia and hypothermia. Hepatic enzyme inducers (carbamazepine, phenytoin, oxcarbazepine, barbiturates, topiramate)—can cause vitamin K deficiency in the infant, with an increased risk of brain haemorrhage. Give vitamin K (phytomenadione) orally 20 mg daily from 36 weeks gestation and 10 mg IV at onset of labour; ensure IM injection (1 mg) given to the infant immediately after birth.

**Status epilepticus**
Prolonged and uncontrolled seizures are associated with a high incidence of serious morbidity and mortality; prompt treatment is required:

- provide basic life support (oxygen by nasal cannula, mask or ventilator; maintenance of BP and blood glucose concentration)
- first give fast acting benzodiazepine to control seizures: usually diazepam (by slow IV injection or rectally if IV access cannot be obtained), or midazolam (IV, IM, intranasal) or clonazepam (IV)
- then give long acting antiepileptic drug (e.g. phenytoin by slow IV injection) to prevent recurrence; monitor BP and ECG during the injection because of the risk of hypotension and arrhythmia
- if status epilepticus persists, give anaesthetic doses of thiopentone, midazolam, or phenobarbitone; assisted ventilation is usually required because of the risk of severe respiratory depression.

**Alcohol withdrawal seizures**

- monitor people at high risk of this condition for signs of withdrawal (pulse rate, BP, mental state)
- benzodiazepines are the preferred treatment; commence loading dose regimen early at first signs of withdrawal; large doses may be required because of increased hepatic metabolism and CNS tolerance.

**Acute brain insult**

- prophylactic antiepileptic drug treatment is not indicated
- antiepileptic drugs used to treat the provoked seizures should be withdrawn unless unprovoked seizures occur later
- antiepileptic drugs are not indicated for seizures occurring immediately after a concussive closed head injury.

**Concentration monitoring**

- monitoring of plasma concentrations may be useful for some antiepileptic drugs (e.g. phenobarbitone, phenytoin, carbamazepine, ethosuximide):
  - early in the course of treatment, to check that the drug concentration is within the target range
  - during the course of treatment, just after a seizure, if dose-dependent adverse effects occur, after a change in dosage, to check compliance and if interacting drugs are started or withdrawn
- Wait until steady-state is reached before monitoring, especially with carbamazepine which autoinduces its metabolism
- Interpret plasma concentrations according to clinical condition; some patients may become seizure-free or experience dose-dependent adverse effects at subtherapeutic concentrations, while others will require and tolerate concentrations beyond the therapeutic range
- Therapeutic ranges are usually based on steady-state trough concentrations; ensure that time of dose and time of sample are considered
- Plasma concentration-effect relationships have not been established for the newer anticonvulsants and are not useful for benzodiazepines and valproate.

**04.08.01 Control of epilepsy**

**CARBAMAZEPINE**

*Mode of action*

Prevents repetitive neuronal discharges through blockade of voltage-dependent and use-dependent sodium channels.

*Indications*

Marketed: Epilepsy, including simple and complex partial seizures, and generalised tonic-clonic seizures, Trigeminal and glossopharyngeal neuralgias, Acute mania and prevention of bipolar disorder.
Accepted: Neuropathic pain.

Contraindications
Hypersensitivity syndrome with carbamazepine, phenytoin, phenobarbitone or oxacarbazepine.
Atrioventricular conduction abnormalities.
History of bone marrow depression.
Porphyria.

Specific considerations
Absence and myoclonic seizure: lack of efficacy and increased risk of seizures.
Treatment with clozapine: increases risk of serious haematological adverse effects; avoid combination or monitor carefully.
Hepatic impairment: Avoid use in severe impairment.

Pregnancy: See also Epilepsy in women in Epilepsy, Increased risk of congenital malformations including spina bifida; risk of haemorrhage in the infant due to vitamin K deficiency; give folic acid (5 mg daily) for at least 1 month before and for 3 months after conception; ADEC category D.

Breastfeeding: Safe to use; monitor infant for drowsiness and poor suckling.

Adverse effects
Common: drowsiness (especially at start of treatment), ataxia, dizziness, blurred vision, diplopia, headache (all dose-related), rash, dry mouth, abdominal pain, nausea, vomiting, anorexia, diarrhoea, constipation, asymptomatic hyponatraemia, leucopenia, thrombocytopenia.
Rare: antibody deficiency, exfoliative dermatitis, Stevens-Johnson syndrome, systemic lupus erythematosus, thrombocytopenia, agranulocytosis, aplastic anaemia; multi-organ hypersensitivity syndrome (including fever, severe skin disease, lymphadenopathy, haematologic abnormalities, hepatitis); psychiatric disorders, SIADH, arrhythmia, orofacial dyskinesia.

Dosage
Epilepsy: Adult, initially 100 mg twice daily, increase daily dose gradually by 100–200 mg every 2–4 weeks according to response. Usual range, 400 mg – 1.2 g daily; up to 2 g daily may be required.
Elderly, debilitated, initially 50 mg twice daily, then increase as above.
Child, initially 5–8 mg/kg daily, increase gradually up to 10–20 mg/kg daily in 2 or more doses.
Trigeminal neuralgia: Initially 50–100 mg once or twice daily, increase gradually up to 400–800 mg daily in 2–4 divided doses. Up to 1.6 g daily may be required.
Neuropathic pain: Initially 100 mg twice daily, increase gradually until pain relieved. Maintenance, 200–600 mg daily, do not exceed 1.2 g daily.
Mania and bipolar disorder: Initially 400 mg daily in divided doses, increase gradually according to response up to 1600 mg daily.

Concentration monitoring
Epilepsy therapeutic range 4–12 mg/L (17–50 micromol/L); measured as steady-state trough plasma concentration.

Patient counselling
Take with food to help prevent stomach upset. Swallow controlled release tablets whole; do not chew or crush them.
This medicine may cause drowsiness, dizziness or blurred vision especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
Carbamazepine may also increase the effects of alcohol.
This medicine interacts with grapefruit and many other drugs; avoid grapefruit and tell your doctor and pharmacist that you are taking carbamazepine before starting any new medication including herbal and over-the-counter products.
Tell your doctor immediately if rash, sore throat, fever, mouth ulcers, bruising or bleeding occur.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
- increase dose slowly to allow for enzyme induction at start of treatment; steady-state plasma concentration may not be achieved for 2–4 weeks because of autoinduction of metabolism
- this also helps improve compliance by minimising severe drowsiness until tolerance develops
- use of controlled release tablets reduces concentration-dependent adverse effects (e.g. dizziness, blurred vision)
- dose may need to be increased slightly when switching to controlled release tablets (same dosing intervals); if switching to liquid, give same total daily dose but at more frequent intervals
- check complete blood picture before treatment; in people with low white cell count, monitor every 2 weeks for the first 1–3 months; stop treatment if leucocyte count is <2–3x10^9 cells/L
monitor for skin reactions; most are transient but some may be serious and life-threatening
women taking carbamazepine should use non-hormonal contraception such as copper-releasing IUD (see Contraception)

Products
CARBAMAZEPINE SYRUP 2 % 250 ML BOTTLE (TEGRETOL®)
CARBAMAZEPINE TABS 200 MG (CARBATOL®, CARBAZINE®, TEGRETOL®)
CARBAMAZEPINE TABS 400 MG CR (TEGRETOL CR®)

CLONAZEPAM
Mode of action
Benzodiazepines potentiate the inhibitory effects of gamma-aminobutyric acid (GABA) throughout the CNS, resulting in anxiolytic, sedative, hypnotic, muscle relaxant and antiepileptic effects.
Indications
Adjunctive treatment for epilepsy refractory to other antiepileptic drugs, in particular absence and myoclonic seizures, infantile spasms, Acute treatment of status epilepticus.
Specific considerations
Pregnancy: See Epilepsy in women in Epilepsy.

Adverse effects
Central nervous system: Drowsiness, fatigue, dizziness, muscle hypotonia, mental changes, and paradoxical aggression.
Others: Hypersalivation in infants, prolonged use may lead to dependence of barbiturate-alcohol type.

Dosage
Epilepsy: Adult, initially, oral 0.5–1 mg at bedtime for 4 days, increase gradually over 2–4 weeks to 2–8 mg daily in divided doses. Child, initially, oral 0.01–0.03 mg/kg in divided doses, increase gradually up to 0.1–0.2 mg/kg daily.
Status epilepticus: Adult, 1 mg by slow IV injection, repeated if necessary. Infant, child, 125–500 micrograms by slow IV injection.

Patient counselling
This medicine may cause drowsiness and affect your ability to drive or operate machinery; avoid these activities until you know how you are affected.
Avoid alcohol or other medications that may cause sedation while taking this drug.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
stop treatment if clear and lasting therapeutic benefit cannot be demonstrated

Products
CLONAZEPAM TABS 0.5 MG (CLONATRIL®, RIVORAM®, RIVOTRIL®)
CLONAZEPAM TABS 2 MG (CLONATRIL®, RIVORAM®, RIVOTRIL®)

GABAPENTIN
Mode of action
Unknown. Structurally related to the neurotransmitter gamma-aminobutyric acid (GABA).
Indications
Partial seizures, with or without secondary generalisation, which are not controlled satisfactorily by other antiepileptic drugs, initially as adjunctive treatment in adults and children >3 years.
Neuropathic pain in adults.
Specific considerations
Absence seizures: risk of aggravation.
Renal impairment: Requires dosage reduction.
Pregnancy: Contact specialised information service; ADEC category B1.
Breastfeeding: No data available.
Adverse effects
Common: fatigue, sedation, dizziness, ataxia, tremor, diplopia, nystagmus, amblyopia, amnesia, abnormal thinking, hypertension, vasodilatation, peripheral oedema, dry mouth, weight increase, rash.
Infrequent: confusion, psychosis, hypoaesthesia, vertigo.
Rare: jaundice, movement disorders, allergic reactions.

Dosage
Adult
Partial seizures, 300 mg on the first day at bedtime, increase by 300 mg daily up to 900–1800 mg daily in 3 divided doses; up to 3600 mg daily in some patients.
Neuropathic pain, initially 100–300 mg at night, increase dose gradually at 3–7 day intervals according to response; usual range 1800–3600 mg daily.

**Child 3–12 years**
Partial seizures, 10 mg/kg daily on the first day, increase by 10 mg/kg daily up to 25–35 mg/kg daily in 3 divided doses; up to 60 mg/kg daily in some children.
Renal impairment: Adjust maintenance dose according to estimated creatinine clearance:
- 60–90 mL/minute, 400 mg 3 times daily
- 30–60 mL/minute, 300 mg twice daily
- 15–30 mL/minute, 300 mg once daily
- <15 mL/minute, 300 mg once every 2 days.

**Haemodialysis**
Loading dose of 300–400 mg, followed by 200–300 mg given after each haemodialysis session.

**Products**
**GABAPENTIN CAPS 300 MG (NEURONTIN®)**

**LAMOTRIGINE**

**Mode of action**
Stabilises presynaptic neuronal membranes by blockade of voltage-dependent and use-dependent sodium channels.

**Indications**
Partial and generalised seizures as adjunctive treatment or monotherapy.

**Contraindications**
Hypersensitivity to lamotrigine.

**Specific considerations**
Myoclonic seizures: risk of aggravation.
Treatment with valproate: increases lamotrigine’s concentration, necessitating lower lamotrigine dose; also increases risk of severe skin reactions.
Hepatic impairment: Not recommended.
Children: Use with caution because of the high risk of severe cutaneous adverse effects; a specialist should begin treatment in in children <2 years.

Pregnancy: Contact specialised information service); ADEC category B3.
Breastfeeding: Excreted in: Breast milk; contact specialised information service).

**Adverse effects**
Common: dizziness, diplopia, ataxia, blurred vision, headache, somnolence, hyperkinesia, nausea, vomiting, maculopapular rash.
Rare:multi-organ hypersensitivity syndrome (e.g. fever, lymphadenopathy, rash, facial oedema, abnormalities of blood and liver, neutropenia, thrombocytopenia.

**Dosage**

**Monotherapy, age >12 years**
Initially, 25 mg once daily for 2 weeks, then 50 mg once daily for 2 weeks. Maintenance, 100–200 mg daily in 1 or 2 doses.

**Adjunctive treatment, age >12 years**
Not taking valproate, initially 50 mg once daily for 2 weeks, followed by 100 mg daily in 2 doses for 2 weeks, then increase by a maximum of 100 mg daily every 1–2 weeks according to clinical response. Maintenance 200–400 mg daily in 2 doses (up to 500–700 mg daily in some patients).

Taking valproate, initially 25 mg every second day for 2 weeks, followed by 25 mg once daily for 2 weeks, then increase by a maximum of 25–50 mg daily every 1–2 weeks according to clinical response. Maintenance 100–
200 mg daily in 1 or 2 doses.

**Adjunctive treatment, age 2–12 years**
Not taking valproate, initially 0.6 mg/kg daily in divided doses for 2 weeks, followed by 1.2 mg/kg daily in divided doses for 2 weeks, then increase by a maximum of 1.2 mg/kg daily every 1–2 weeks according to clinical response. Maintenance, 5–15 mg/kg daily in divided doses to a maximum of 400 mg daily.

Taking valproate, initially 0.15 mg/kg once daily for 2 weeks, followed by 0.3 mg/kg once daily for 2 weeks, then increase by a maximum of 0.3 mg/kg daily every 1–2 weeks according to clinical response. Maintenance, 1–5 mg/kg once daily or in divided doses to a maximum of 200 mg daily
Patient counselling
Tablets may be swallowed whole, chewed or dispersed in a small volume of water.
This medicine may cause drowsiness, dizziness or blurred vision; if affected, do not drive or operate machinery.
Lamotrigine may also increase the effects of alcohol.
Tell your doctor immediately if you develop a rash, fever or swollen glands.
Do not stop taking this medicine suddenly unless your doctor tells you to...

Practice points
- stop treatment immediately if skin reaction or signs of hypersensitivity occur (with or without rash); if stopping treatment for other reasons gradually reduce the dose over 2 weeks.

Products
LAMOTRIGINE TABS 5 MG (LAMICTAL®)
LAMOTRIGINE TABS 25 MG (LAMICTAL®)
LAMOTRIGINE TABS 100 MG (LAMICTAL®, LAMOGEN®)

LEVETIRACETAM
Experience with this drug is limited; previously unreported adverse effects or drug interactions may occur.

Mode of action
Unknown.

Indications
Adjunctive treatment for partial seizures with or without secondary generalisation.

Specific considerations
Renal impairment: Reduce dosage, measure creatinine clearance before dose selection.
Hepatic impairment: Reduce dosage in severe impairment.
Pregnancy: No human data; ADEC category B3.
Breastfeeding: Excreted in breast milk; avoid use.

Adverse effects
Common: somnolence, asthenia, dizziness, headache, amnesia, ataxia, convulsion, depression, emotional lability, hostility, insomnia, nervousness, tremor, diplopia, rash, anorexia, diarrhoea, dyspepsia, nausea.

Dosage
Adult, adolescent >16 years
Initially, 500 mg twice daily; then increase dose, according to response, by 500 mg twice daily at 2–4 week intervals, up to 1500 mg twice daily.
Renal impairment: Adjust dose according to estimated creatinine clearance:
50–79 mL/minute, 500–1000 mg twice daily
30–49 mL/minute, 250–750 mg twice daily
<30 mL/minute, 250–500 mg twice daily
Dialysis, 500–1000 mg once daily: a 250–500 mg supplemental dose is recommended following dialysis.
Hepatic impairment: 250–750 mg twice daily in severe impairment when creatinine clearance is <70 mL/minute.

Patient counselling
This medicine may make you feel drowsy or dizzy especially at the start of treatment or when the dose is increased; if affected, do not drive or operate machinery.
Levetiracetam may also increase the effects of alcohol.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
- once seizures are controlled using levetiracetam as adjunctive therapy, consider its use as monotherapy

Products
LEVETIRACETAM TABS 500 MG (KEPPRA®)

PHENYTOIN

Mode of action
Prevents repetitive neuronal discharge through blockade of voltage-dependent and use-dependent sodium channels.

Indications
Epilepsy, including simple partial and complex seizures, and generalised tonic-clonic seizures.
Status epilepticus (IV).

Contraindications
Previous hypersensitivity syndrome with phenytoin, carbamazepine or phenobarbitone
Porphyria.
Sinus bradycardia, sinoatrial block, second and third degree atrioventricular block, Stokes–Adams syndrome (IV).

**Specific considerations**
Absence and myoclonic seizures: lack of efficacy.
Diabetes: risk of hyperglycaemia.
Hepatic impairment: May require dosage reduction.
Pregnancy: See Epilepsy in women.
Consult specialised information service); increased risk of congenital malformations; haemorrhage may occur in infants due to vitamin K deficiency; ADEC category D.
Breastfeeding: May be used.

**Adverse effects**
Common: nausea, vomiting, insomnia, agitation; sedation, confusion, ataxia, nystagmus, diplopia, blurred vision, vertigo, behavioural disturbances, impaired learning (dose-related); gingival hypertrophy, skin eruption, coarse facies, hirsutism (long term use), IV, hypotension, thrombophlebitis, skin necrosis
Rare: hallucinations, peripheral neuropathy, choreiform movements, cerebellar atrophy, blood dyscrasias, hyperglycaemia, osteomalacia and rickets, Stevens–Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus, multi-organ hypersensitivity syndrome (including fever, severe skin disease, lymphadenopathy, haematologic abnormalities, hepatitis), IV, CNS depression, ventricular dysrhythmia

**Dosage**

**Epilepsy**
Adult, oral, initially 4–5 mg/kg daily in 1 or 2 doses, increase by 30 mg daily once every 2 weeks according to clinical response and plasma concentration. Usual range, 200–500 mg daily.
Child, oral, initially 5 mg/kg daily in 1 or 2 doses, increase gradually according to clinical response and plasma concentration. Maintenance, 4–8 mg/kg daily in 2 or 3 doses; higher doses may be required in young children and infants.

**Status epilepticus**
Adult, IV 15–20 mg/kg. An additional dose of 5 mg/kg may be given after 12 hours if necessary.
Child, IV 15–20 mg/kg.

**Dose equivalence**
100 mg phenytoin sodium contains approximately 92 mg phenytoin.
Phenytoin capsules and injection are available as phenytoin sodium, while the tablets and suspension contain phenytoin.

**Concentration monitoring**
Therapeutic range, 10–20 mg/L (40–80 micromol/L).
A small change in dosage may result in a disproportionately large change in phenytoin concentration because of saturation of its hepatic metabolism; the dose can be increased by 100 mg daily if plasma phenytoin concentration is 5 mg/L or less, but by no more than 30 mg daily if concentration is higher.
Measurement of free phenytoin (not bound to albumin) is recommended in patients with decreased albumin and chronic renal failure.

**Administration instructions**
Give IV injection slowly (<50 mg/minute in adults and <25 mg/minute in the elderly) and avoid extravasation.
Do not give IV injection with glucose 5%, to avoid crystallisation of phenytoin; IV injection can be diluted with sodium chloride 0.9% to a concentration of 5 mg/mL; flush the needle or catheter with sodium chloride 0.9% after injection to avoid local venous irritation.
Avoid IM injection because of erratic bioavailability.

**Patient counselling**
Phenytoin may make you feel drowsy or dizzy; if affected, do not drive or operate machinery.
This medicine may also increase the effects of alcohol.
Phenytoin interacts with many other drugs; ask your doctor or pharmacist before using any other medicine including herbal and over-the-counter products.
Visit your dentist regularly; good dental care can help prevent phenytoin causing enlarged gums.
Tell your doctor immediately if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding occur.
Do not stop taking this medicine suddenly unless your doctor tells you to.

**Practice points**
- consider monitoring phenytoin concentration if changing from a product containing phenytoin to one containing phenytoin sodium (and vice versa), see Dose equivalence
• check phenytoin concentration and withdraw temporarily and/or reduce dosage if neurological adverse effects are present
• where a decision is made to withdraw treatment, do so preferably over 6 months at a rate not greater than 25 mg each week or 100 mg each month
• monitor BP, ECG and respiratory function during IV injection; reduce the rate of administration if seizures stop before full dose is given, or if arrhythmia, hypotension or venous irritation occurs
• women taking phenytoin should use non-hormonal contraception such as copper-releasing IUD (see Contraception)

Products
PHENYTOIN SODIUM CAPS/TABS 100 MG (DI-HYDAN®, EPANUTIN®)
PHENYTOIN SODIUM SUSP. 30 MG/5ML 100 ML BOTTLE (NOT REGISTERED)
PHENYTOIN SODIUM VIAL 50 MG/VIAL (PHENTOLEP®)

PRIMIDONE
Mode of action
Prolong inhibitory postsynaptic potential by increasing the mean chloride channel opening time and hence the duration of gamma-aminobutyric acid (GABA)-induced cell membrane hyperpolarisation.

Indications
Epilepsy, including simple and complex partial seizures, generalised tonic-clonic seizures.

Contraindications
Hypersensitivity syndrome with carbamazepine, phenytoin or phenobarbitone.
Acute porphyria.

Specific considerations
Respiratory disease: risk of respiratory depression.
Renal impairment: May require a dose reduction.
Hepatic impairment: May require a dose reduction.
Elderly: Use with caution; increased risk of adverse effects; reduce initial dose by 30–50%.
Children: Use with caution; risk of behavioural changes and hyperactivity.
Pregnancy: See also Epilepsy in women in Epilepsy
Brestfeeding: Avoid use; risk of sedation in infant.

Adverse effects
Prolonged use may cause physical dependence.
Common: rash, sedation, confusion, depression, cognitive impairment, altered mood and behaviour, paradoxical insomnia, hyperactivity and aggression (particularly in children)
IV, hypotension, respiratory depression
Infrequent: nystagmus, ataxia
Rare: exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis, megaloblastic anaemia, osteomalacia, Dupuytren's contracture, frozen shoulder, generalised pain (long term use), multi-organ hypersensitivity syndrome (including fever, severe skin disease, lymphadenopathy, haematologic abnormalities, hepatitis), IV, skin necrosis (extravasation).

Dosage
Adult, initially 125 mg daily at bedtime; gradually increase daily dose by 125 mg every 3 days to a total of 250 mg twice daily; then increase daily dose by 250 mg every 3 days to a maximum of 1.5 g daily in divided doses.
Child, initially 5 mg/kg at bedtime; gradually increase to 10–20 mg/kg daily in 2 divided doses; maximum dose 750 mg daily.

Patient counselling
This medicine may cause drowsiness and affect your ability to drive or operate machinery; avoid these activities until you know how it affects you.
Avoid taking alcohol as it may worsen the side effects of phenobarbitone/primidone.
This medicine interacts with many other drugs; ask your doctor or pharmacist before using any other medicine including herbal and over-the-counter products.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
• steady-state plasma concentration may not be achieved for 2–4 weeks
• tolerance to sedation develops with continued administration
• women taking barbiturates should use non-hormonal contraception such as copper-releasing IUD (see Contraception)

**Products**
PRIMIDONE TABS 250 MG (NOT REGISTERED)

**TOPIRAMATE**

**Mode of action**
In epilepsy, topiramate stabilises presynaptic neuronal membranes by blocking voltage-dependent sodium channels. Enhances activity of gamma-aminobutyric acid (GABA) on postsynaptic chloride channels.

**Indications**
Partial seizures with or without secondary generalisation, generalised tonic-clonic seizures and drop attacks associated with Lennox–Gastaut syndrome (adjunctive treatment or monotherapy)
Prevention of migraine in adults

**Specific considerations**
History of psychiatric disorders: topiramate is associated with many psychiatric adverse effects.
Personal or family history of nephrolithiasis and hypercalciuria: increased risk of nephrolithiasis; ensure adequate hydration.
Predisposition to acidosis (e.g. severe respiratory or renal disease, status epilepticus): may increase risk of metabolic acidosis.
Renal impairment: May require reduction in maintenance dose and a longer interval between dose adjustments as it takes longer to reach steady-state concentrations. Risk of metabolic acidosis may be increased.
Pregnancy: Contact specialised information service ADEC category B3.
Breastfeeding: Excreted in breast milk; contact specialised information service).

**Adverse effects**
Common: somnolence, headache, confusion, amnesia, impaired concentration, depression, emotional lability, nervousness, agitation, hallucinations, paraesthesia, dizziness, fatigue, speech disorder, reduced serum bicarbonate (see Metabolic acidosis), nephrolithiasis, weight loss, leucopenia.
Infrequent: psychosis, suicidal ideation, aphasia, nystagmus, diplopia, taste disturbance, nausea, rash
Rare: hepatitis, decreased sweating and hyperthermia, metabolic acidosis, acute myopia (with secondary acute closed angle glaucoma).

Metabolic acidosis: Topiramate inhibits renal carbonic anhydrase which commonly leads to a dose-related decrease in serum bicarbonate concentrations and rarely to hyperchloraemic, non-ion gap, metabolic acidosis. Chronic untreated metabolic acidosis may increase risk of kidney stones, osteomalacia and osteoporosis, and in children may lead to rickets and reduced growth rate.

**Dosage**
Daily doses of 50 mg or more should be taken in 2 divided doses.

**Adult**
Epilepsy, adjunctive treatment: Initially, 25–50 mg once daily as a single dose at bedtime (or in 2 doses); then increase daily dose at intervals of at least a week by 25–100 mg. Maintenance, 100–200 mg twice daily. Maximum 1000 mg daily.
Epilepsy, monotherapy: Initially, 25 mg once daily at bedtime; then increase daily dose at intervals of at least a week by 25–50 mg. Maintenance, 50 mg twice daily. Maximum 500 mg daily.
Migraine prophylaxis: Initially, 25 mg daily as a single dose at bedtime; then increase daily dose at intervals of at least a week by 25 mg, according to response. Maintenance, 25–50 mg twice daily.

**Child >2 years**
Epilepsy, adjunctive treatment: Initially, 1–3 mg/kg daily (up to 25) mg daily as a single dose at bedtime; increase daily dose at intervals of at least a week by 1–3 mg/kg. Maintenance, 5–9 mg/kg daily in 2 divided doses. Maximum 30 mg/kg daily.
Epilepsy, monotherapy: Initially, 0.5–1 mg/kg daily as a single dose at bedtime; increase daily dose by intervals of at least a week by 0.5–1 mg/kg. Maintenance, 3–6 mg/kg daily in 2 divided doses. Maximum 500 mg daily.

**Patient counselling**
Topiramate may make you feel drowsy or dizzy especially when you start treatment or the dose is increased; if affected, do not drive or operate machinery.
Avoid taking alcohol as it may worsen some of the side effects of topiramate.
Tell your doctor immediately if your eyesight changes or you have eye pain.
Do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
- stop treatment as quickly as possible if acute onset of decreased visual acuity or ocular pain occur
- monitor for decreased sweating and hyperthermia, especially in hot weather; risk is increased if combined with other drugs with this effect, e.g. anticholinergics
- measure serum bicarbonate concentration at baseline and periodically during treatment.

Products
TOPIRAMATE TABS 25 MG (TOPAMAX®)
TOPIRAMATE TABS 100 MG (TOPAMAX®)

VALPROIC ACID

Mode of action
Prevents repetitive neuronal discharge by blocking voltage-dependent and use-dependent sodium channels.

Indications
Marketed: Primary generalised epilepsy (including absence, tonic-clonic, myoclonic and atonic seizures), and simple and complex partial seizures
Bipolar disorder when other treatments have failed
Accepted: Prevention of recurrent migraine when other treatments have failed.

Contraindications
Pancreatic dysfunction, porphyria, urea cycle disorders

Specific considerations
Hepatic impairment: Avoid use in severe impairment.
Surgery: Check platelet count and INR before surgery.
Pregnancy: Contact specialised information service); ADEC category D.
Breastfeeding: Safe to use at low dosage.

Adverse effects
Common: nausea, vomiting, increased appetite, weight gain, tremor, paraesthesia, drowsiness, ataxia, elevated liver transaminase concentrations.
Infrequent: thinning or loss of scalp hair (usually temporary), menstrual irregularities, abnormal bleeding time, rash, hyperammonaemia.
Rare: hepatic failure (especially in young children with neurological abnormality or taking multiple drugs), leucopenia, thrombocytopenia, pancreatitis, extrapyramidal syndrome, peripheral oedema.

Dosage
Epilepsy: Adult, initially 15 mg/kg daily in 1 or 2 doses, increase at 2-week intervals by 200 mg daily according to response. Usual maintenance dose 20–30 mg/kg daily, maximum 2.5 g daily.
Infant, child, initially 15 mg/kg daily in 2–3 divided doses, increase according to response. Usual maintenance dose 20–30 mg/kg daily.
Bipolar disorder: Adult, initially 600 mg daily, increase at 3-day intervals by 200 mg daily according to response. Maintenance dose 1000–2000 mg (20–30 mg/kg) daily.
Prevention of migraine: Adult, 200–400 mg twice daily.

Concentration monitoring
There is poor correlation between therapeutic efficacy and plasma concentration but concentrations may be useful to confirm toxicity or compliance.
Epilepsy only therapeutic range, 40–100 mg/L (280–700 micromol/L); up to 150 mg/L (1000 micromol/L) in some people. Measure as trough plasma concentration. Steady-state concentration may be achieved after 3–5 days.

Patient counselling
There is poor correlation between therapeutic efficacy and plasma concentration but concentrations may be useful to confirm toxicity or compliance.
Epilepsy only, therapeutic range, 40–100 mg/L (280–700 micromol/L); up to 150 mg/L (1000 micromol/L) in some people. Measure as trough plasma concentration. Steady-state concentration may be achieved after 3–5 days.

Practice points
- routine monitoring of liver transaminase concentrations does not predict the rare occurrence of hepatic failure
- stop treatment promptly if there is loss of seizure control, anorexia, vomiting, ataxia, impaired consciousness, jaundice or oedema that may be indicative of hepatitis or pancreatitis
• stop treatment if spontaneous bruising or bleeding occurs; this may indicate thrombocytopenia, effect on clotting factors or hepatotoxicity
• use of enteric coated tablets may minimise GI adverse effects.

Products
VALPROIC ACID CAPS/TABS 200 MG (CONVULEX®, DEPAKINE®, EPIVAL®)
VALPROIC ACID CAPS 300 MG (CONVULEX®)
VALPROIC ACID SYRUP 200 MG/5ML 100 ML BOTTLE (EPIVAL®)
VALPROIC ACID VIALS (NOT REGISTERED)
VALPROIC ACID+SODIUM VALPROATE CAPS/TABS 500 MG (CONVULEX®, DEPAKINE®, EPIVAL®)

04.09 DRUGS FOR PARKINSONISM

PARKINSON'S DISEASE

Rationale for drug use
Provide symptomatic relief.

Before starting treatment
When tremor is the main symptom, consider other conditions, e.g. hyperthyroidism or essential tremor.
If diagnosis of parkinsonism is established, consider causes other than idiopathic Parkinson's disease, e.g. other neurodegenerative disorders, drug-induced parkinsonism.

When to start treatment
Decision to begin drug treatment depends on the patient's personal situation and expectations and is usually deferred until the symptoms become physically or socially disabling. No agent has been proven to slow progression of disease.

Drug choice
The available drugs aim to redress the balance between the dopaminergic deficiency and relative cholinergic excess in the brain by either increasing dopamine or acting as dopamine agonists or anticholinergics.
Start with a low dose taken with the evening meal and increase gradually to improve mobility while minimising adverse effects.

Levodopa
Improves bradykinesia and rigidity more consistently than tremor.
First line treatment for most people, especially the elderly and people with cognitive impairment.
Only available with a peripheral dopa decarboxylase inhibitor (carbidopa or benserazide) to decrease peripheral metabolism of levodopa to dopamine (which does not cross the blood-brain barrier). Combination allows a reduction in levodopa dosage, with subsequent decrease in peripheral dopamine adverse effects (e.g. nausea, vomiting, hypotension).
Long term use is associated with increased motor fluctuations (end-of-dose failure and on-off effect), dyskinesias and dystonias. Their development may relate to duration of levodopa treatment and/or reflect disease progression.

Dopamine agonists
Bromocriptine, Cabergoline, Pergolide
Improve bradykinesia and rigidity, but are less effective than levodopa.
May cause confusion and hallucinations more commonly than levodopa, especially in elderly or demented people, and in high doses.
Combination of dopamine agonists with levodopa allows a reduction in levodopa dosage and improves motor fluctuations.
Cabergoline or bromocriptine used as monotherapy in early disease may delay the onset of motor fluctuations and dyskinesias and may be preferred as first line treatment in younger patients. However, adverse effects associated with the high doses needed, long term risk of retroperitoneal and pleuropulmonary fibrosis, and the gradual loss of efficacy, limit their long term use as monotherapy. Pergolide is marketed for use only as an adjunct to levodopa. Efficacy and safety of dopamine agonists seem broadly similar. Cabergoline has a longer duration of action than bromocriptine and pergolide and can be given once daily.

Apomorphine
Useful in people severely disabled by motor fluctuations refractory to conventional treatment. May allow a reduction in levodopa dosage.
Start treatment in hospital under specialist supervision. Administer by SC injection or continuous infusion with portable pump.
Is highly emetogenic and requires pretreatment with domperidone to reduce nausea. See Practice points.

Selegiline
May be used as monotherapy in early disease to delay the need for levodopa and as adjunct to levodopa in later disease to reduce motor fluctuations (evidence for its effectiveness is inconclusive). The dose of levodopa may need to be reduced.

Although 2 studies found an increased mortality associated with selegiline use, this was not confirmed in a recent meta-analysis of the use of monoamine oxidase type B inhibitors in early Parkinson's disease.

**Amantadine**

Has dopaminergic and anticholinergic activity; more effective than anticholinergic drugs for akinesia and rigidity, but less effective for tremor. Some loss of efficacy after 3–6 months.

May be used as monotherapy in early disease or later as adjunctive treatment to alleviate drug-induced dyskinesias.

**Entacapone**

May be used as an adjunct to levodopa in patients with motor fluctuations. It increases duration of motor improvement ('on' time), but also increases levodopa-induced dyskinesias and GI adverse effects. The dose of levodopa may need to be reduced. There are limited data available for use with controlled release formulations of levodopa.

Combination preparations of entacapone with levodopa/carbidopa are available.

**Anticholinergic drugs**

Include benzhexol, benztropine, biperiden and orphenadrine.

Modest effect on tremor, but little effect on rigidity and bradykinesia.

May be used as monotherapy in early disease when tremor is predominant, or as adjunctive treatment in patients inadequately controlled by levodopa.

Used infrequently because of the incidence of adverse effects and relatively poor efficacy. Avoid use in the elderly and those with cognitive impairment.

Withdraw slowly to avoid precipitating a cholinergic crisis.

**Management of non-motor symptoms**

Symptoms such as autonomic dysfunction (orthostatic hypotension, constipation, neurogenic bladder disturbances, sexual dysfunction), depression, cognitive decline (and eventually dementia), sensory complaints and pain are associated with Parkinson's disease and may require treatment.

Recent studies have shown that treatment of dementia in Parkinson's disease with anticholinesterases may be of some benefit.

Psychosis is rare in untreated disease and appears to be predominantly drug-induced. Reduce dose of antiparkinsonian agents and simplify drug regimen if possible, otherwise consider using clozapine or quetiapine.

Conventional antipsychotics (dopamine antagonists) may worsen Parkinson's disease.

**Practice points**

- Abrupt withdrawal of some antiparkinsonian drugs has been associated with symptoms resembling the neuroleptic malignant syndrome; reduce dose gradually
- Domperidone, a dopamine antagonist that does not cross the blood-brain barrier and is not expected to worsen parkinsonism, helps to reduce nausea and vomiting; avoid agents such as prochlorperazine and metoclopramide (central dopamine antagonist activity).

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**04.09.01 Dopaminergic drugs**

**AMANTADINE**

**Mode of action**

Increases dopamine release and blocks cholinergic receptors; acts as a N-methyl-D-aspartate (NMDA) antagonist in the glutamatergic pathway from subthalamic nucleus to globus pallidus. Antiviral activity against some strains of influenza.

**Indications**

Parkinson's disease, Prevention of influenza type A in non-immunised people.

**Specific considerations**

- Epilepsy: increases risk of seizures.
- Heart failure, recurrent eczema, glaucoma, prostatic enlargement, confusion, hallucinations, psychosis, peptic ulcer disease, orthostatic hypotension: risk of aggravation.
- Treatment with dopamine antagonists (e.g. conventional antipsychotics): may worsen control of Parkinson's disease; avoid combination.
- Treatment with drugs with anticholinergic effects, see Table 04-08 Drugs with anticholinergic effects: increases anticholinergic effect; monitor clinical effect.
- Renal impairment: Reduce dose.
Elderly: May require dosage reduction.
Pregnancy: Limited data available; ADEC category B3.
Breastfeeding: Contact specialised information service).

Adverse effects
Common: nervousness, depression, nightmares, insomnia, hallucinations, dizziness, headache, blurred vision, orthostatic hypotension, peripheral oedema, livedo reticularis, dry mouth, nausea, vomiting, constipation.
Infrequent: urinary retention, dermatitis, heart failure.
Rare: confusion, corneal lesions.

Dosage
Parkinson's disease: Adult 65 years and under, 100 mg daily, increase after at least a week to 100 mg twice daily.
>65 years, 100 mg once daily.
Influenza: 10–65 years: 100 mg twice daily for 5–7 days.
>65 years, or child 5–9 years, 100 mg once daily for 5–7 days.

Patient counselling
Take with food to reduce stomach upset.
Be careful when you stand up as this medicine might make you feel dizzy if you stand up too quickly.
Parkinson's disease, do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points
- do not stop amantadine abruptly in Parkinson's disease; reduce dose gradually because of the risk of symptoms resembling neuroleptic malignant syndrome (fever, muscle rigidity, rhabdomyolysis, profuse sweating, tachycardia, tachypnoea, agitation).

Products
AMANTADINE TABS 100 MG (AS SULFATE) (PK-MERZ®)

LEVODOPA WITH BENSERAZIDE OR CARBIDOPA

Mode of action
Levodopa is converted to dopamine in the brain and peripheral tissues, and replenishes depleted striatal dopamine. It is given with a peripheral dopa decarboxylase inhibitor (benserazide or carbidopa) to reduce peripheral dopamine production and also reduce adverse effects (e.g. nausea, vomiting, hypotension).

Indications
Parkinson's disease.

Contraindications
Closed angle glaucoma.

Specific considerations
Peptic ulcer disease, melanoma, cardiovascular disease, cardiac arrhythmia, psychiatric disorders: risk of aggravation.
Open angle glaucoma: mydriasis may cause slight increase in intraocular pressure.
Treatment with dopamine antagonists (e.g. conventional antipsychotics): may worsen control of Parkinson's disease; avoid combination.

Pregnancy: Limited data available; ADEC category B3.
Breastfeeding: Avoid use if possible; may inhibit lactation.

Adverse effects
Common: anorexia, nausea, vomiting, orthostatic hypotension, dyskinesia, episodes of sudden unpredictable loss of mobility (‘off’ effect); agitation, insomnia, sudden sleep onset, somnolence, depression, hallucination and confusion (especially in the elderly).
Infrequent: dark discolouration of urine and sweat, angina, cardiac arrhythmias, GI bleeding.
Rare: allergic reactions including angioedema, urticaria.

Dosage
Dosage is expressed as levodopa.

Conventional products
Initially 50 mg twice daily, adjust gradually according to response. Maintenance, 300–800 mg daily in 3 or more divided doses.

Controlled release products
Conversion to Madopar HBS®, initially use the same daily levodopa dose and same dosage frequency; increase dose every 2–3 days according to response to an average increase of 50% over original levodopa dose; titration may take up to 4 weeks.
Conversion to Sinemet CR®, initially increase daily levodopa dose by 10% and give in divided doses every 4–
12 hours (intervals <4 hours are not recommended). Adjust dose and/or dosing interval every 3 days according to response; may need to give up to 30% more than original levodopa dose.

**Patient counselling**
Take this medicine at the same time each day and in the same way (eg always before food). This medication may cause drowsiness; if affected do not drive or operate machinery. Be careful when you stand up as this medicine might make you feel dizzy if you stand up too quickly. Do not stop taking this medicine suddenly unless your doctor tells you to. Carbidopa and entacapone combination: do not break tablets in half as they may not work properly.

**Practice points**
- levodopa-benserazide and levodopa-carbidopa preparations are available in the ratio 4:1; levodopa-carbidopa preparations are also available in the ratio 10:1
- a daily minimum of 75 mg carbidopa is required to inhibit peripheral decarboxylation significantly
- increasing the dose of benserazide or carbidopa may help to reduce peripheral adverse effects (e.g. flushing, hypotension, nausea, anorexia); daily doses of carbidopa >200–300 mg confer no further benefit
- food reduces the absorption of levodopa but it may be given with food initially to minimise GI effects; in later stages of the disease it may be better to give levodopa on an empty stomach to minimise fluctuations
- dispersible tablets may be useful if swallowing is difficult or to achieve a rapid response, particularly in early morning stiffness
- do not withdraw levodopa abruptly because of the risk of withdrawal syndrome resembling the neuroleptic malignant syndrome (fever, muscle rigidity, rhabdomyolysis, profuse sweating, tachycardia, tachypnoea, agitation).

**Controlled release products**
- release levodopa over a longer period (4–6 hours) but have a lower oral bioavailability than conventional preparations
- may improve end-of-dose motor fluctuations in people with diminishing response to levodopa; may also be useful for nocturnal off-periods or early morning akinesia; conventional product may still be required for the first dose in the morning because of its faster onset of action

**Products**
- CARBIDOPA 25 MG+LEVODOPA 100 MG TABS (SINEMET®)
- CARBIDOPA 25 MG+LEVODOPA 250 MG TABS (CREDANIL®, LEVOCAR®, SINEMET®)

04.09.02 Anticholinergic drugs used in parkinsonism

**BIPERIDEN**

**Mode of action**
Block muscarinic actions of acetylcholine to produce a wide range of effects including:
- reduction of relative excess of cholinergic activity that accompanies dopamine deficiency in Parkinson's disease.
- reduction of salivation and gastric secretions; inhibition of intestinal motility.
- reduction of bladder muscle contractility and increase in bladder capacity.
- tachycardia.
- mydriasis and cycloplegia.
- bronchodilation and decrease in bronchial secretions.

Structural variation within the class confers some differences in site of action and adverse effects. Tertiary amines act centrally and peripherally and have the full range of adverse effects, including antinicotinic action at higher doses. Quaternary amines are less active orally and tend to have fewer CNS effects.

**Indications**
Parkinson's disease.
Drug-induced extrapyramidal disorders (except tardive dyskinesia).

**Contraindications**
Closed angle glaucoma, GI obstruction or atony, Urinary obstruction, Myasthenia gravis.

**Specific considerations**
Heart disease (including arrhythmias, coronary heart disease, heart failure): may be exacerbated.
Prostatic hypertrophy: symptoms may worsen.
Inflammatory bowel disease: risk of paralytic ileus.
Gastro-oesophageal reflux: may be aggravated.
Fever, high ambient temperature: risk of hyperthermia.

Treatment with drugs with anticholinergic effects: additive anticholinergic effects; increases therapeutic and adverse effects; avoid combination.

Elderly: Use with caution as elderly people are more sensitive to adverse anticholinergic effects; confusion may be precipitated or worsened. Start with low dosage and increase slowly to the lowest effective dose.

Children: Use with caution; more susceptible to adverse anticholinergic effects. Some drugs are not recommended (see individual monographs).

Pregnancy: Contact specialised information service; ADEC category B2.

Breastfeeding: Limited data available; contact specialised information service.

Adverse effects

Usually dose-related and reflect pharmacological action. The frequency of adverse effects depends on the drug's structure as well as patient (e.g. co-morbidity, age). They include:

- rash
- dry mouth
- constipation
- dyspepsia
- nausea
- vomiting
- blurred vision
- dry eyes
- tachycardia
- urinary retention
- dizziness
- drowsiness
- headache
- hallucinations
- memory impairment
- confusion
- insomnia
- worsening of dyskinesia
- generalised choreic movements
- fever due to anhidrosis

Rare: anaphylaxis.

Dosage

- Parkinson's disease: 1 mg twice daily, increase gradually up to 1–4 mg 3–4 times daily.
- Drug-induced extrapyramidal disorders: 1–2 mg 1–4 times daily.

Patient counselling

This medicine may cause drowsiness, dizziness or blurred vision and may increase the effects of alcohol; if affected, do not drive or operate machinery.

Parkinson's disease, do not stop taking this medicine suddenly unless your doctor tells you to.

Practice points

- although also marketed for pyramidal spasticity, closed craniocerebral trauma, post-concussion symptoms, trigeminal neuralgia and nocturnal cramps, biperiden is not recommended for these indications
- dry mouth may reduce ability to adhere to fluid restriction in heart failure and severe renal failure
- may precipitate closure of anterior angle with risk of glaucoma; monitor intraocular pressures at regular intervals
- avoid stopping treatment abruptly in Parkinson's disease to prevent an acute exacerbation; also risk of cholinergic crisis

Products

- BIPERIDEN TABS 2 MG (AS HCL) (AKINETON®)
- PROCYCLIDINE AMPS 10 MG/AMP (AS HCL) 2 ML AMP (KEMADRIN®)

04.09.03 Other drugs for Parkinson's disease
**BOTULINUM TOXIN**

**Mode of action**
Neurotoxin produced by *Clostridium botulinum*. Botulinum toxin type A irreversibly inhibits acetylcholine released at the neuromuscular junction; produces local flaccid paralysis for about 2–3 months until new motor endplates form.

**Indications**
Marketed: Blepharospasm, Hemifacial spasm, Glabellar lines, Spasticity of the arm following a stroke, Equinus foot deformity in cerebral palsy, Cervical dystonia (spasmodic torticollis), Primary hyperhidrosis of the axillae, Focal spasticity.
Accepted: Strabismus, Laryngeal dystonia, Oromandibular dystonia.

**Contraindications**
Myasthenia gravis.

**Specific considerations**
Pregnancy: Avoid use; ADEC category B3.
Breastfeeding: Contact specialised information service.

**Adverse effects**
Common: pain, weakness of muscle groups adjacent to site of injection, dysphagia, falls, Blepharospasm, ptosis, eye irritation, increased lacrimation.
Infrequent: paralysis of distant muscles (misplaced injections or excessive doses), diplopia, entropion, ectropion, keratitis.

**Dosage**
Botulinum toxin should be used only by specially trained physicians; see manufacturer's product information.

**Practice points**
- units expressing the potency of the 2 botulinum toxin preparations available are not equivalent therapeutically; preparations are not interchangeable
- resistance to treatment may occur in some people; this may be caused by antibodies to botulinum toxin; use the lowest dose that gives an adequate clinical response and make periods between injections as long as possible

**Products**
BOTULINUM TOXIN VIAL 100-500 IU (BOTOX®, DYSPORT®)

**ENTACAPONE**

**Mode of action**
Inhibits catechol-O-methyltransferase (COMT), mainly in peripheral tissues; increases the amount of levodopa available to the brain and prolongs the clinical response to levodopa.

**Indications**
Parkinson's disease as an adjunct to levodopa in patients with motor fluctuations.

**Contraindications**
Phaeochromocytoma, History of neuroleptic malignant syndrome, Non-traumatic rhabdomyolysis, Hepatic impairment. Manufacturer contraindicates use with MAOIs or with a combination of a MAO-A and a MAO-B inhibitor.

**Specific considerations**
Pregnancy: No data available; ADEC category B3.
Breastfeeding: No data available; avoid use.

**Adverse effects**
Common: nausea, vomiting, dry mouth, diarrhoea, abdominal pain, constipation, discoloured urine, hallucination, confusion, paranoia, dyskinesia.
Rare: increase in liver enzymes.

**Dosage**
200 mg with each levodopa-carbidopa or levodopa-benserazide dose, up to 2 g daily.

**Patient counselling**
This medicine may increase some side effects of levodopa such as:
- dizziness (if you stand up too quickly)
- drowsiness (if affected, do not drive or operate machinery).
- do not stop taking entacapone suddenly unless your doctor tells you to.
Practice points
- do not stop entacapone abruptly, because of the risk of withdrawal syndrome resembling the neuroleptic malignant syndrome (fever, muscle rigidity, rhabdomyolysis, profuse sweating, tachycardia, tachypnoea, agitation)
- reduce daily dose of levodopa by about 10–30% to decrease dopaminergic adverse effects, e.g. dyskinesia.

Products
ENTACAPONE TABS 200 MG (COMTAN®)

ORPHENADRINE

Mode of action
Block muscarinic actions of acetylcholine to produce a wide range of effects including:
- reduction of relative excess of cholinergic activity that accompanies dopamine deficiency in Parkinson's disease
- reduction of salivation and gastric secretions; inhibition of intestinal motility
- reduction of bladder muscle contractility and increase in bladder capacity
- tachycardia
- mydriasis and cycloplegia
- bronchodilation and decrease in bronchial secretions.

Structural variation within the class confers some differences in site of action and adverse effects. Tertiary amines act centrally and peripherally and have the full range of adverse effects, including antinicotinic action at higher doses. Quaternary amines are less active orally and tend to have fewer CNS effects.

Indications
Accepted: Parkinson's disease.
Drug-induced extrapyramidal disorders (except tardive dyskinesia).

Contraindications
Closed angle glaucoma, GI obstruction or atony, Urinary obstruction, Myasthenia gravis.

Specific considerations
Heart disease (including arrhythmias, coronary heart disease, heart failure): may be exacerbated.
Prostatic hypertrophy: symptoms may worsen.
Inflammatory bowel disease: risk of paralytic ileus.
Gastro-oesophageal reflux: may be aggravated.
Fever, high ambient temperature: risk of hyperthermia.
Treatment with drugs with anticholinergic effects: additive anticholinergic effects; increases therapeutic and adverse effects; avoid combination.
Elderly: Use with caution as elderly people are more sensitive to anticholinergic adverse effects; confusion may be precipitated or worsened. Start with low dosage and increase slowly to the lowest effective dose.
Children: Use with caution; more susceptible to anticholinergic adverse effects. Some drugs are not recommended (see individual monographs).
Pregnancy: Atropine Contact specialized information centre; ADEC category B2.

Adverse effects
Usually dose-related and reflect pharmacological action. The frequency of adverse effects depends on the drug's structure (see Mode of action) as well as the patient (e.g. age, co-morbidity).
rash, dry mouth, constipation, nausea, vomiting, dyspepsia, blurred vision, mydriasis, dry eyes, urinary retention, tachycardia, arrhythmia, dizziness, drowsiness, headache, hallucinations, memory impairment, confusion, insomnia, worsening of dyskinesia, generalised choreic movements, fever due to anhidrosis, anaphylaxis.

Dosage
Initially 100 mg twice daily; increase gradually if required. Maximum 400 mg daily.

Patient counselling
This medicine may cause drowsiness, dizziness or blurred vision and may increase the effects of alcohol; if affected, do not drive or operate machinery.
Parkinson's disease, do not stop this medicine suddenly unless your doctor tells you to.

Practice points
- rarely used for above indications
- only marketed use is for muscle spasm; efficacy for this indication is not well established
- halve tablet, e.g. by using a tablet cutter, if more flexibility in dosing is needed, e.g. 50 mg 3 times daily
- dry mouth may reduce ability to adhere to fluid restriction in heart failure and severe renal failure
may precipitate closure of anterior angle with risk of glaucoma; monitor intraocular pressures at regular intervals

avoid stopping treatment abruptly in Parkinson's disease to prevent an acute exacerbation; also risk of cholinergic crisis.

Products

ORPHENADRINE AMPS 30 MG/AMP (AS CITRATE) (NOT REGISTERED)

PIRACETAM

Mode of action

Piracetam acts on the CNS and has been described as a 'nootropic'; it is said to protect the cerebral cortex against hypoxia. It is also reported to inhibit platelet aggregation and reduce blood viscosity at high doses. Piracetam is used as an adjunct in the treatment of myoclonus of cortical origin. It has also been used in dementia. Other disorders or states in which it has been tried (on the basis of a supposed 'cerebrocortical insufficiency' responsive to piracetam) include alcoholism, vertigo, cerebrovascular accidents, dyslexia, behavioural disorders in children, and after trauma or surgery.

Adverse Effects and Precautions

Piracetam is reported to produce insomnia or somnolence, weight gain, hyperkinesia, nervousness, and depression. Diarrhoea and rashes may occur at a lower frequency. Piracetam should not be given to patients with hepatic impairment or severe renal impairment; dosage reductions are recommended for patients with lesser degrees of renal impairment. Therapy with piracetam should not be withdrawn abruptly.

Dosage

In cortical myoclonus, piracetam is given in doses of 7.2 g daily increasing by 4.8 g daily every 3 or 4 days up to a maximum of 20 g daily. It is given by mouth in 2 or 3 divided doses. Once the optimal dose of piracetam has been established, attempts should be made to reduce the dose of other drugs. Piracetam has been given for various other disorders in doses of 0.8 to 1 g three times daily by mouth. In severe disorders it has been given by intramuscular or intravenous injection.

Administration in renal impairment.

Dosage should be reduced in patients with mild to moderate renal impairment according to creatinine clearance (CC):

<table>
<thead>
<tr>
<th>CC (mL/minute)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-40</td>
<td>Half the usual dose</td>
</tr>
<tr>
<td>40-20</td>
<td>One-quarter of the usual dose</td>
</tr>
</tbody>
</table>

Dementia.

Although piracetam is used in some countries in the management of cognitive impairment and dementia, a recent systematic review concluded that the evidence from the published literature did not support this use.

Stroke.

Piracetam did not influence the outcome if given within 12 hours of the onset of acute ischaemic stroke in a multicentre, randomised, double-blind trial, although post hoc analyses suggested that it might confer benefit when given within 7 hours of onset, particularly in patients with stroke of moderate to severe degree. Further analyses of the same data concluded that piracetam did not produce significant adverse effects when given in high doses to patients with acute stroke, and significantly more patients had recovered from aphasia on piracetam than placebo. The results of two further randomised, double-blind, placebo-controlled trials supporting the role of piracetam as an adjunct to intensive speech therapy in improving aphasia following stroke were also reported. In contrast, a review of the first study considered that the trend towards an increased risk of early death in patients allocated to piracetam was of concern, and concluded that the data did not support routine use of piracetam in acute ischaemic stroke.

Products

PIRACETAM AMPS 1 GM/AMP   5 ML AMP (MEMOTAL®, NOOTROPIL®)
PIRACETAM CAPS 400 MG (NORCETAM®)
PIRACETAM ORAL SOLUTION 200 MG/ML  200 ML BOTTLE (NOOTROPIL®)
PIRACETAM TABS 800 MG (NOOTROPIL®, NORCETAM®)

04.10 ACETYLCHELINESTERASE INHIBITORS

04.10.01 Drugs for myasthenia gravis
PYRIDOSTIGMINE

Mode of action
Reduce breakdown of neuronally released acetylcholine by inhibiting cholinesterase; enhance neuromuscular transmission in skeletal and smooth muscles.

Indications
Myasthenia gravis, Reversal of neuromuscular blockade induced by non-depolarising neuromuscular blockers.

Contraindications
Intestinal or urinary obstruction.

Specific considerations
Asthma, cardiovascular disorders (including arrhythmia, bradycardia, hypotension), seizures, Parkinson's disease, peptic ulcer: risk of aggravation.
Renal impairment: Requires dose reduction.
Pregnancy: Seek specialist advice; neostigmine ADEC category B2, pyridostigmine ADEC category C.
Breastfeeding: Safe to use; monitor infant for muscular weakness.

Adverse effects
Common: increased salivation, nausea, vomiting, diarrhoea, abdominal cramps
Infrequent: rash, anaphylaxis
Overtreatment: May lead to a cholinergic crisis with increased cholinergic effects (e.g. excessive sweating, miosis, involuntary defecation and urination, nystagmus, bradycardia, hypotension, increased muscle weakness leading to fasciculation and paralysis), CNS effects (e.g. ataxia, convulsions, agitation, coma) and death due to respiratory failure or cardiac arrest.
Distinction between a cholinergic crisis (overtreatment) and a myasthenic crisis (undertreatment) may be difficult (especially if an anticholinergic drug is used to relieve adverse effects), and may require an edrophonium test.

Dosage
Adult: Conventional tablet, initially 60 mg once daily; adjust dosage according to duration of action up to 300–720 mg daily in divided doses. Controlled release tablet, 180–540 mg (1–3 tablets) once or twice daily.
Child: Conventional tablet, increase gradually up to 7 mg/kg daily in divided doses. Controlled release tablet, 90–180 mg once daily at bedtime.

Practice points
- atropine (0.25 mg SC/IM) or oral propantheline may be necessary to minimise muscarinic adverse effects at the beginning of treatment, but should not be given routinely because they may mask signs of overtreatment.
- transient resistance may occur after prolonged treatment; decrease dosage or withdraw drug for several days under medical supervision.

Products
PYRIDOSTIGAMINE TABS 60 MG (AS BROMIDE) (MESTINON®)

04.10.02 Drugs for Alzheimer's disease

ALZHEIMER'S DISEASE
Accumulation of beta-amyloid peptide appears to be central to the degenerative changes seen in the brain in Alzheimer's disease. It results in the destruction of cholinergic neurones and a fall in acetylcholine concentration. None of the available drugs prevents Alzheimer's disease or modifies its pathology.
Anticholinesterases and memantine (an N-methyl-D-aspartate antagonist), are approved for the treatment of Alzheimer's disease. At best, they show modest efficacy in improving cognition and/or reducing the rate of cognitive and functional decline; their clinical usefulness and effect on quality of life remains uncertain.
The optimal duration of treatment with these drugs is unclear, but there is some evidence that patients may benefit from anticholinesterases for up to 3 years.
Specialists are also beginning to use combination treatment. A recent study in patients with moderate-to-severe disease receiving a stable dose of donepezil, showed that adding memantine improved cognitive and functional outcomes compared with donepezil alone.
Evidence is lacking for other approaches, including anti-amyloid therapies, antioxidants and anti-inflammatory agents.

Management of neuropsychiatric symptoms
Always consider non-drug interventions first. Drug treatment is not particularly effective. Few randomised controlled trials have addressed the optimal drug management of non-cognitive symptoms in Alzheimer's disease. Consider the risks and benefits for each patient.
Antipsychotics are often used. They have modest efficacy in the treatment of agitation or psychosis, but are associated with substantial adverse effects (including increased risk of stroke). Mood stabilisers (e.g. carbamazepine, valproate) or antidepressants may be beneficial in some patients. Anticholinesterases, the small improvement in neuropsychiatric symptoms reported in some trials is of uncertain clinical significance. Treatment of depression, particularly with SSRIs, may be useful. Drugs with anticholinergic effects (Table 4-8) should be avoided. Review the need for continuing drug treatment regularly. Some behavioural disturbances may be transient.

**DONEPEZIL**

**Mode of action**
Decrease breakdown of acetylcholine and thereby reduce the apparent deficiency of cholinergic neurotransmitter activity in Alzheimer's disease.

**Indications**
Mild-to-moderate Alzheimer's disease.

**Contraindications**
Active peptic ulcer, GI or ureteric obstruction.

**Specific considerations**
History of peptic ulcer disease, seizures (including sick sinus syndrome), heart block, bradyarrhythmia, Parkinson's disease, asthma, obstructive pulmonary disease: risk of aggravation. Treatment with drugs with anticholinergic effects, antagonises therapeutic effect; avoid combination.

**Adverse effects**
Common: nausea, vomiting, diarrhoea, anorexia, abdominal pain, dyspepsia, headache, insomnia, vivid dreams, fatigue, depression, dizziness, drowsiness, tremor, weight loss, muscle cramps, urinary incontinence, increased sweating.

**Dosage**
Initially 5 mg once daily for a minimum of 4 weeks. Increase to 10 mg once daily according to clinical response.

**Counselling**
Take in the evening just before bedtime.

This medicine may cause dizziness or drowsiness; if you are affected, avoid operating machinery.

**Practice points**
- dose of 10 mg daily appears to provide marginally more benefit than 5 mg daily but increases risk of adverse effects.
- omit 1 or more doses if adverse effects occur; reduce to previous well-tolerated dose if adverse effects persist.
- if treatment is interrupted for several days, restart at initial dosage to minimise the risk of severe vomiting.

**Products**
DONEPEZIL TABS 5 MG (AS HCL) (ARICEPT®)

**RIVASTIGMINE**

**Mode of action** Indications, Contraindications, Adverse effects, and practice points
As for donepezil.

**Specific considerations**
Renal impairment
Reduced clearance; titrate to maximum tolerated dose.

Hepatic impairment
Reduced clearance; titrate to maximum tolerated dose.

**Patient counselling**
Take with morning and evening meals.
This medicine may cause dizziness or drowsiness; if you are affected, avoid operating machinery.
Dosage
Initially 1.5 mg twice daily; increase by 3 mg daily every 2 weeks to a maximum dose of 6 mg twice daily.

Practice points
- omit 1 or more doses if adverse effects occur, reduce to previous well-tolerated dose if adverse effects persist.
- if treatment is interrupted for several days, restart at initial dosage to minimise the risk of severe vomiting.

Products
RIVASTIGMIN CAPS 1.5 GM (EXELON®)

04.11 DRUGS USED IN SUBSTANCE DEPENDENCE, ALCOHOL DEPENDENCE

DISULFIRAM

Mode of action
Deters alcohol use. Disulfiram prevents the usual metabolism of alcohol (irreversibly inhibits aldehyde dehydrogenase), blocking acetaldehyde breakdown, which causes unpleasant, potentially serious effects if alcohol is consumed, e.g. flushing, sweating, nausea, vomiting, headache, dyspnoea, palpitations, chest pain, hypotension, cardiovascular collapse, convulsions, arrhythmias.

Indications
Maintenance of abstinence in alcohol dependence.

Contraindications
Allergy to disulfiram or thiuram derivatives (some pesticides, rubber products), Ischaemic heart disease, Severe myocardial disease, Psychosis, Severe hepatic or renal disease.

Specific considerations
Treatment with isoniazid or metronidazole—increases risk of toxic reactions; avoid combinations.

Pregnancy: Safety not established; avoid use; ADEC category B2.

Breastfeeding: Safety not established; avoid use.

Adverse effects
Common: drowsiness, nausea, headache, fatigue.
Infrequent: taste disturbance (metallic or garlic-like).
Rare: jaundice, hepatitis (sometimes fatal), peripheral neuropathy, psychosis, confusion, optic neuritis, blood dyscrasias, rash.

Dosage
Initially, 100 mg daily for 1–2 weeks; maintenance, 200 mg daily. Maximum, 300 mg daily.

Patient counseling
If you notice yellowing of the whites of your eyes, dark urine or pale bowel motions, stop taking disulfiram and tell your doctor at once.

Unpleasant effects may occur after taking very small amounts of alcohol used in cooking or even if rubbed into the skin (e.g. avoid alcohol-containing aftershave, perfumes, body lotions, vinegar and alcohol-containing medicines).

Practice points
- consider only if patient is likely to be deterred from drinking by fear of unpleasant effects, and someone is available to supervise daily administration
- do not start disulfiram unless the patient fully understands the risks involved and has not consumed alcohol in the previous 24 hours
- after stopping treatment new enzyme must be synthesised before metabolism of alcohol returns to normal (usually 7–10 days, but may take 3 weeks)
- patients may experience adverse effects if they drink alcohol within 7 days after stopping treatment
- there is marked individual variation in response to alcohol—some react to very small amounts; others have little reaction despite consuming large doses of alcohol.

Products
DISULFIRAM TABS 200 MG (NOT REGISTERED)

04.12 DRUGS USED IN MULTIPLE SCLEROSIS TREATMENT
**INTERFERON BETA**

**Mode of action**
Thought to act through immunoregulatory actions including antagonism of gamma interferon, reduction of cytokine release and augmentation of suppressor T-cell function.

**Indications**
Ambulatory people with multiple sclerosis with >2 relapses in previous 2 years.
Secondary progressive multiple sclerosis

**Contraindications**
History of severe depression with or without suicidal ideation, Decompensated hepatic disease, Inadequately controlled epilepsy.

**Specific considerations**
Seizure disorders: risk of exacerbation or recurrence.
Cardiac disease, e.g. heart failure: may worsen.
Pregnancy: Contraindicated (spontaneous abortions in some trials); ADEC category D.
Breastfeeding: No data available.

**Adverse effects**
Common: pain and inflammation at injection site (with SC injections), flu-like symptoms (severity and incidence decrease with continued administration), headache, depression, nausea, abdominal pain, raised liver enzymes, anaemia.
Infrequent: interferon beta neutralising antibodies (commonly develop after 18–24 months), hypertension
Rare: palpitations, heart failure, cardiomyopathy, suicidal thoughts, confusion, autoimmune disorders, neutropenia, leucopenia, thrombocytopenia, lymphadenopathy, hepatotoxicity, thyroid dysfunction, hypersensitivity, hair loss, necrosis at injection site.

**Dosage**
Treatment should continue for at least 2 years.
Interferon beta-1a: IM, 30 micrograms (6x106 units) once a week., SC, gradually increase dose over 4 weeks to 44 micrograms (12x106 units) 3 times a week, if not tolerated reduce to 22 micrograms (6x106 units) 3 times a week.
Interferon beta-1b: SC, 250 micrograms (8x106 units) every 2 days (3 doses each week).
Interferon-1b SC, 250 micrograms (8x106 units) every 2 days (3 doses each week)

**Patient counseling**
Tell your doctor immediately if you are feeling more depressed or sad than usual.
Rotate injection sites to help prevent irritation.

**Practice points**
- affects relapse incidence, may not affect disability
- minimise flu-like reaction by dosing at bedtime and premedicating with paracetamol
- These products contain human albumin; inform patient of the possibility of transmission of infectious agents (including as yet unidentified agents).

**Monitoring**
- monitor complete blood count and liver function at baseline, at 1, 3 and 6 months, then periodically
- consider reducing dose if ALT concentration rises >5 times upper limit of normal; stop treatment if symptoms of liver disease occur.

**Products**
- INTERFERON-BETA VIAL 8 M IU/VIAL (AVONEX®)
- INTERFERON-BETA VIAL 12 M IU/VIAL (REBIF®)
Table 04-01 Comparative characteristics of antipsychotic drugs

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional antipsychotics</td>
<td>all conventional antipsychotics can cause hyperprolactinaemia</td>
</tr>
<tr>
<td></td>
<td>still conventional antipsychotics can cause hyperprolactinaemia</td>
</tr>
<tr>
<td>chlorpromazine, thioridazine, pericyazine</td>
<td>most sedating; most potent anticholinergic effects; least likely to cause EPSE; most likely to cause orthostatic hypotension; sometimes referred to as 'low potency' antipsychotics</td>
</tr>
<tr>
<td>trifluoperazine, fluphenazine</td>
<td>moderately sedating; intermediate propensity to cause EPSE; some potential to cause orthostatic hypotension</td>
</tr>
<tr>
<td>haloperidol, droperidol, thiothixene, pimozide</td>
<td>least sedating; almost no anticholinergic effects; most likely to cause EPSE; least likely to cause orthostatic hypotension; sometimes referred to as 'high potency' antipsychotics</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>atypical antipsychotics have less potential for EPSE than conventional agents, but depends on dose</td>
</tr>
<tr>
<td>amisulpride</td>
<td>hyperprolactinaemia, EPSE, less potential for weight gain and sedation</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>may cause insomnia; less potential for hyperprolactinaemia</td>
</tr>
<tr>
<td>clozapine</td>
<td>effective in treatment-resistant patients but has serious adverse effects (blood dyscrasias, seizures, cardiomyopathy, myocarditis, orthostatic hypotension, sedation, weight gain); potential for important drug interactions with fluvoxamine, fluoxetine (enhanced toxicities) related to clozapine; may cause sedation, weight gain, peripheral oedema; increased risk of</td>
</tr>
<tr>
<td>olanzapine</td>
<td>stroke and related mortality in elderly dementia patients; important drug interactions similar to clozapine</td>
</tr>
<tr>
<td>quetiapine</td>
<td>sedating and vasoactive, less potential for hyperprolactinaemia</td>
</tr>
<tr>
<td>risperidone</td>
<td>EPSE; orthostatic hypotension and hyperprolactinaemia may be a problem; increased risk of</td>
</tr>
<tr>
<td></td>
<td>of stroke and related mortality in elderly dementia patients; important drug interactions similar to clozapine</td>
</tr>
</tbody>
</table>

Table 04-02 Drugs that may contribute to the serotonin syndrome

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>antidepressants</td>
<td>TCAs, MAOIs (including moclobemide), SSRIs, mirtazapine, venlafaxine, St John's Wort</td>
</tr>
<tr>
<td>opioids</td>
<td>tramadol, pethidine, dextromethorphan</td>
</tr>
<tr>
<td>stimulants</td>
<td>phentermine, diethylpropion, hallucinogenic amphetamines, sibutramine</td>
</tr>
<tr>
<td>5HT1 agonists</td>
<td>sumatriptan, naratriptan, zolmitriptan</td>
</tr>
<tr>
<td>others</td>
<td>illicit drugs (e.g. 'ecstasy', LSD, cocaine), selegiline, tryptophan, buspirone, lithium, linezolid</td>
</tr>
</tbody>
</table>
### Table 04-03 Antidepressant changeover guide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rationale</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category A changeover</strong></td>
<td>fluoxetine, phenelzine, tranylcypromine</td>
<td>drug (or metabolites) with long half-life or persistent effects</td>
</tr>
<tr>
<td><strong>Category B changeover</strong></td>
<td>TCAs, SSRIs (except fluoxetine), mianserin, mirtazapine</td>
<td>drug (or metabolites) with intermediate half-life of 24–48 hours</td>
</tr>
<tr>
<td><strong>Category C changeover</strong></td>
<td>moclobemide, reboxetine, venlafaxine</td>
<td>drug (or metabolites) with short half-life of &lt;18 hours</td>
</tr>
</tbody>
</table>

### Table 04-04 Features of antidepressant withdrawal syndromes

<table>
<thead>
<tr>
<th>Class</th>
<th>Withdrawal effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCAs</strong></td>
<td>cholinergic rebound: hypersalivation, runny nose, abdominal cramping, diarrhoea, sleep disturbance</td>
<td>more common with amitriptyline, doxepin, trimipramine</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td>dizziness, nausea, paraesthesia, anxiety, agitation, tremor, sweating, confusion, electric shock-like sensations</td>
<td>more common with paroxetine and least likely with fluoxetine</td>
</tr>
<tr>
<td><strong>others</strong></td>
<td>venlafaxine may cause a syndrome similar to that seen with SSRIs</td>
<td>particularly likely with venlafaxine because of its short elimination half-life</td>
</tr>
</tbody>
</table>

### Table 04-05 Pain types and analgesia

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Nociceptive, e.g. fracture</th>
<th>Neuropathic, e.g. post-herpetic neuralgia</th>
<th>Inflammatory, e.g. rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>paracetamol</td>
<td>effective; most useful when taken regularly at maximal recommended doses</td>
<td>less effective</td>
<td>effective but no anti-inflammatory effect</td>
</tr>
<tr>
<td>opioids</td>
<td>effective</td>
<td>may be effective (depends on choice and dose)</td>
<td>may be effective (depends on dose)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>effective</td>
<td>not effective</td>
<td>Effective</td>
</tr>
<tr>
<td>TCAs, parenteral local anaesthetics, antiepileptics, clonidine</td>
<td>rarely used (clonidine may be effective as adjunct)</td>
<td>may be effective</td>
<td>rarely used (may be effective as adjunct)</td>
</tr>
</tbody>
</table>
### Table 04-06 Opioid comparative information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Suggested dose equivalent to 10 mg IM/SC morphine$^1$</th>
<th>Approximate duration of action (hours)$^2$</th>
<th>Adjust dose in renal impairment$^3$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>codeine$^4$</td>
<td>130 mg IM; 200 mg oral</td>
<td>3–4</td>
<td>yes</td>
<td>mild-to-moderate pain; do not exceed 60 mg single dose</td>
</tr>
<tr>
<td>dextropropoxyphene$^4$ unknown</td>
<td>4–6</td>
<td>yes</td>
<td></td>
<td>mild-to-moderate pain; avoid long term use</td>
</tr>
<tr>
<td>fentanyl</td>
<td>100–150 mcg IV/SC</td>
<td>0.5–1</td>
<td>no</td>
<td>moderate-to-severe acute or chronic pain; preferred in renal impairment</td>
</tr>
<tr>
<td>hydromorphone$^4$</td>
<td>1.5–2 mg SC/IM; 6–7.5 mg oral</td>
<td>2–4</td>
<td>yes</td>
<td>moderate-to-severe acute or chronic pain</td>
</tr>
<tr>
<td>methadone</td>
<td>10 mg SC/IM; 20 mg oral$^b$</td>
<td>8–24 (chronic dosing)</td>
<td>no</td>
<td>severe chronic pain; management of opioid dependence</td>
</tr>
<tr>
<td>morphine$^4$</td>
<td>30 mg oral</td>
<td>2–3; 12–24 (controlled release)</td>
<td>yes</td>
<td>moderate-to-severe acute or chronic pain</td>
</tr>
<tr>
<td>oxycodone</td>
<td>15–20 mg oral</td>
<td>3–4; 12–24 (controlled release)</td>
<td>yes</td>
<td>moderate-to-severe acute or chronic pain</td>
</tr>
<tr>
<td>pethidine$^4$</td>
<td>75–100 mg IM</td>
<td>2–3</td>
<td>contraindicated</td>
<td>not recommended</td>
</tr>
<tr>
<td>tramadol$^4$</td>
<td>100–120 mg IM/IV; 150 mg oral</td>
<td>3–6</td>
<td>yes</td>
<td>moderate-to-severe pain</td>
</tr>
<tr>
<td><strong>Partial agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>buprenorphine</td>
<td>0.4 mg IM; 0.8 mg sublingual</td>
<td>6–8</td>
<td>no</td>
<td>not recommended for analgesia; management of opioid dependence</td>
</tr>
</tbody>
</table>

$^1$doses given are guidelines only

$^2$duration of action depends on dose and route of administration; if pain occurs, give more frequently (except for controlled release products)

$^3$refer to monographs for details of dosage adjustment

$^4$active metabolite; see monograph

$^b$based on single dose studies, see Dose equivalence in Methadone for chronic use of methadone
Table 04-07 Choice of antiepileptic drug

<table>
<thead>
<tr>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td></td>
</tr>
<tr>
<td>carbamazepine</td>
<td>gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbitone, phenytoin, pregabalin, tiagabine, topiramate, valproate</td>
</tr>
<tr>
<td>Generalised tonic-clonic</td>
<td>lamotrigine, oxcarbazepine, phenobarbitone, phenytoin, topiramate</td>
</tr>
<tr>
<td>valproate, carbamazepine</td>
<td>clobazam, clonazepam, lamotrigine</td>
</tr>
<tr>
<td>Absence</td>
<td></td>
</tr>
<tr>
<td>valproate, ethosuximide</td>
<td>clobazam, clonazepam, lamotrigine</td>
</tr>
<tr>
<td>Myoclonic</td>
<td></td>
</tr>
<tr>
<td>valproate</td>
<td>clobazam, clonazepam, phenobarbitone</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td></td>
</tr>
<tr>
<td>tetracosactrin (ACTH analogue), prednisolone</td>
<td>clonazepam, nitrazepam, valproate, vigabatrin1</td>
</tr>
</tbody>
</table>

1use only if no safer alternative

Table 04-08 Drugs with anticholinergic effects

This table should be used with the background information about the drug/s which appears before the list of its interactions.

Drugs with anticholinergic effects

- amantadine, amitriptyline, atropine, azatadine
- belladonna alkaloids, benzhexol, benztoprine, biperiden, brompheniramine
- chlorpheniramine, chlorpromazine, clomipramine, clozapine, cyclopentolate, cyproheptadine
- dexchlorpheniramine, dimenhydrinate, diphenhydramine, disopyramide, dothiepin, doxepin
- glycopyrrolate
- homatropine, hyoscine (scopolamine)
- imipramine, ipratropium (nebulised)
- methdilazine, mianserin
- nortriptyline
- orphenadrine, oxybutynin
- pericyazine, pheniramine, pimozide, pizotifen, procainamide, promethazine, propantheline
- quinidine
- thioridazine, tiotropium, tolterodine, trimeprazine, trimipramine, triprolidine, tropicamide
CHAPTER 05 INFECTIONS

05.01 ANTIBACTERIAL DRUGS

Choice of a suitable drug
Before selecting an antibacterial the clinician must first consider two factors: the patient and the known or likely causative organism. Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (i.e. whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking an oral contraceptive.

The known or likely organism and its antibacterial sensitivity, in association with the above factors, will suggest one or more antibacterials, the final choice depending on the microbiological, pharmacological, and toxicological properties. An example of a rational approach to the selection of an antibacterial is treatment of a urinary-tract infection in a patient complaining of nausea in early pregnancy. The organism is reported as being resistant to ampicillin but sensitive to nitrofurantoin (can cause nausea), gentamicin (can be given only by injection and best avoided in pregnancy), tetracycline (causes dental discoloration) and trimethoprim (folate antagonist therefore theoretical teratogenic risk), and cefalexin. The safest antibiotics in pregnancy are the penicillins and cefalosporins; therefore, cefalexin would be indicated for this patient.

The principles involved in selection of an antibacterial must allow for a number of variables including changing renal and hepatic function, increasing bacterial resistance, and new information on side-effects. Duration of therapy, dosage, and route of administration depend on site, type and severity of infection and response.

Antibacterial policies
Local policies often limit the antibacterials that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

Before starting therapy
The following precepts should be considered before starting:

- Viral infections should not be treated with antibacterials. However, antibacterials are occasionally helpful in controlling secondary bacterial infection (e.g. acute necrotising ulcerative gingivitis secondary to herpes simplex infection);
- Samples should be taken for culture and susceptibility testing; ‘blind’ antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- Knowledge of prevalent organisms and their current susceptibility is of great help in choosing an antibacterial before bacteriological confirmation is available;
- The dose of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection. The prescribing of the so-called ‘standard’ dose in serious infections may result in failure of treatment or even death of the patient; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored.
- The route of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections require intravenous therapy. Whenever possible, painful intramuscular injections should be avoided in children.
- Duration of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because they promote the emergence of resistance, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or chronic osteomyelitis it is necessary to treat for prolonged periods. Conversely a single dose of an antibacterial may cure uncomplicated urinary-tract infections.

Oral bacterial infections
Antibacterial drugs should be prescribed for the treatment of oral infections only on the basis of defined need. They may be used in conjunction with, but not as an alternative to, other appropriate measures, such as providing drainage or extracting a tooth.
The ‘blind’ prescribing of an antibacterial for unexplained pyrexia, cervical lymphadenopathy, or facial swelling can lead to difficulty in establishing the diagnosis. Bacteriological sampling should always be carried out in severe oral infections.

Oral infections which call for antibacterial treatment include acute suppurative pulpitis, acute periapical or periodontal abscess, cellulitis, oral-antral fistula (and acute sinusitis), severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destructive forms of chronic periodontal disease. Most of these infections are readily resolved by the early establishment of drainage and removal of the cause (typically an infected necrotic pulp). Antibacterials may be indicated if treatment has to be delayed and they are essential in immunocompromised patients or in those with conditions such as diabetes or Paget’s disease. Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving fascial spaces such as Ludwig’s angina, require antibiotics and specialist hospital care.

Antibacterial drugs may also be useful after dental surgery in some cases of spreading infection. Infection may spread to involve local lymph nodes, to fascial, where it can cause airway obstruction, or into the bloodstream, where it can lead to cavernous sinus thrombosis and other serious complications. Extension of an infection can also lead to maxillary sinusitis; osteomyelitis is a complication, which usually arises when host resistance is reduced. If the oral infection fails to respond to antibacterial treatment within 48 hours, the antibacterial should be changed, preferably on the basis of bacteriological investigation. Failure to respond may also suggest an incorrect diagnosis, lack of essential additional measures (such as drainage), poor host resistance, or poor patient compliance. Combination of a penicillin, or erythromycin, with metronidazole may sometimes be helpful for the treatment of severe or resistant oral infections.

Superinfection

In general, broad-spectrum antibacterial drugs such as the cephalosporins are more likely to be associated with adverse reactions related to the selection of resistant organisms e.g. fungal infections or antibiotic-associated colitis (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

Therapy

Suggested treatment is shown in table 1. When the pathogen has been isolated, treatment may be changed to a more appropriate antibacterial if necessary. If culture for bacteria is negative, the antibacterial can be continued or stopped on clinical grounds.

05.01.01 Penicillins

The penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. They are excreted in the urine in therapeutic concentrations.

The most important side-effect of the penicillins is hypersensitivity which manifests in the form of rashes and anaphylaxis that can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals; anaphylactic reactions occur in fewer than 0.05% of treated patients. Patients with a history of atopic allergy (e.g. asthma, eczema, hay fever) are at a higher risk of severe anaphylactic reactions to penicillins.

Patients who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure. Individuals with a history of a minor rash (i.e. non-confluent rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind.

A rare but serious toxic effect of the penicillins is encephalopathy due to cerebral irritation. This may result from excessively high doses or in patients with severe renal failure. The penicillins should not be given by intrathecal injection because they can cause encephalopathy which may be fatal.

Another problem relating to high doses of penicillin, or normal doses given to patients with renal failure, is the accumulation of electrolyte since most injectable penicillins contain either sodium or potassium. Diarrhoea frequently occurs during oral penicillin therapy. It is most common with broad-spectrum penicillins, which can also cause antibiotic-associated colitis.

05.01.01.01 Benzylpenicillin and Phenoxymethylpenicillin

**BENZATHINE PENICILLIN**

Beta-lactamase labile

**Mode of action**
Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**
Prophylaxis of rheumatic fever, Infections susceptible to prolonged low concentrations of benzylpenicillin, e.g. early or latent syphilis
Treatment or prevention of infection caused by susceptible bacteria

**Contraindications**
Allergy to penicillins, Cefalosporins or carbapenems

**Specific considerations:**
Syphilis (and other spirochetal infections): Jarisch–Herxheimer reaction can occur after starting treatment.
Sodium restriction, cardiac failure: some parenteral penicillins, eg benzylpenicillin, piperacillin and ticarcillin with clavulanic acid, have high sodium content and in high doses can precipitate cardiac failure in patients with poor cardiac reserve.
Infectious mononucleosis: High incidence of rash.
Renal impairment: High parenteral doses and/or prolonged treatment may result in electrolyte disturbance and neurotoxicity (convulsions, coma), due to accumulation of the penicillin.
Pregnancy: All penicillins are considered safe to use; ADEC category A.
Breastfeeding: safe; it may cause loose bowel actions in the infant.

**Adverse effects:**
Penicillins are generally well tolerated.
Accidental intravascular administration: Severe neurovascular damage. CNS effects including anxiety, agitation, fear of death and hallucinations. These effects usually resolve in 15–30 minutes, but rarely last for up to 24 hours.
Jarisch–Herxheimer reaction: Fever, chills, headache, hypotension and flare-up of lesions (due to release of pyrogens from the organisms) can occur shortly after starting to treat syphilis or other spirochete infections. Can be dangerous in cardiovascular syphilis or where there is serious risk of local damage, e.g. optic atrophy; lasts for 12–24 hours; symptoms can be alleviated by aspirin or prednisolone.
Common: diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site (less common with benzylpenicillin), superinfection (including candidiasis) especially during prolonged treatment with broad spectrum penicillins, allergy
Infrequent: fever, vomiting, erythema, exfoliative dermatitis, angioedema, pseudomembranous colitis
Rare: anaphylactic shock, bronchospasm, interstitial nephritis, serum sickness-like syndrome, blood dyscrasias, electrolyte disturbances, neurotoxicity, bleeding, haemolytic anaemia, haemolytic uraemic syndrome (high dose and/or renal impairment), nephropathy (with parenteral use), Stevens–Johnson syndrome, toxic epidermal necrolysis

**Dosage**
Adult, IM, single dose of 0.9–1.8 g. Maximum 1.8 g given as 2 injections at separate sites.
Child, IM, 225–675 mg given as a single injection.
Prophylaxis of recurrent rheumatic fever: Adult, child, IM, 900 mg every 3–4 weeks.
Early syphilis (primary, secondary or latent), IM, 1.8 g as a single dose.
Late latent syphilis (in the absence of neurosyphilis) IM, 1.8 g once each week for 3 doses.
Dose equivalence: 1.8 g = 2.4 million units.

**Administration instructions**
Give by deep IM injection only (do not give IV). Give doses >900 mg as 2 injections at separate sites.
IV penicillins are physically incompatible with many substances (including aminoglycosides); give separately.
Avoid rapid IV administration of large doses as it may result in seizures.
Lignocaine can be used to reconstitute IM injections to reduce local pain.

**Practice points**
- absorbed slowly into circulation and hydrolysed to benzylpenicillin; use when prolonged, low concentrations of benzylpenicillin are appropriate and adequate
- In adults duration of effect of 900 mg dose is 2–4 weeks.
- syringes are not graduated; part syringe dosing is not accurate but is used
- use frequent doses of penicillins for maximal antibacterial effect
- monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days)
- avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven (ESCAPPM,
**BENZYL-PENICILLIN**

Beta-lactamase labile. Also known as penicillin G.

**Mode of action**

Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**

Bacterial endocarditis, Meningitis, Aspiration pneumonia, lung abscess, Community-acquired pneumonia, Syphilis, Septicaemia in children

**Contraindications**

Allergy to penicillins, Cefalosporins or carbapenems

**Specific considerations**

Same as Benzathine Penicillin

**Adverse effects:**

Same as Benzathine Penicillin

**Dosage:**

Adult, IV, 0.6–1.2 g every 4–6 hours. Maximum 18 g daily (e.g. endocarditis, meningitis); higher doses may be used on specialist advice.

Child, IM/IV, 30–60 mg/kg every 4–6 hours.

Severe renal impairment: Adult, maximum 3.6 g daily.

Suspected meningococcal meningitis before hospitalization: Give dose after collecting blood for culture.

Adult, child 10 years and over, IV/IM, 1.2 g.

Child 1–9 years, IV/IM, 600 mg.

Child <1 year, IV/IM, 300 mg.

Tertiary syphilis (including neurosyphilis): 1.8 g IV every 4 hours for 15 days with prednisolone to reduce Jarisch–Herxheimer reaction

Dose equivalence: 600 mg = 1 million units.

**Administration instruction**

IV penicillins are physically incompatible with many substances (including aminoglycosides); give separately. Avoid rapid IV administration of large doses as it may result in seizures.

Lignocaine can be used to reconstitute IM injections to reduce local pain.

**Practice points**

- contains 3.4 mmol (78 mg) sodium per 1.2 g injection
- use frequent doses of penicillins for maximal antibacterial effect
- monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days)
- avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven

**Products**

BENZYL-PENICILLIN SODIUM VIAL 1,000,000 IU/VIAL (PEN G®)

**PHENOXYMETHYL-PENICILLIN**

Beta-lactamase labile. Also known as penicillin V

**Mode of action**

Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**

S. pyogenes tonsillitis/pharyngitis or skin infections. Prophylaxis of rheumatic fever. Moderate-to-severe gingivitis (with metronidazole)

Treatment or prevention of infection caused by susceptible bacteria

**Contraindications**

Allergy to penicillins, Cefalosporins or carbapenems

**Specific considerations**

Same as Benzathine Penicillin

**Adverse effects**
Same as Benzathine Penicillin

**Dosage**

Adult, 250–500 mg every 6–8 hours. Maximum 3 g daily.
Child, 10–12.5 mg/kg every 6 hours.
Prophylaxis of recurrent rheumatic fever (long term), Adult, child >5 years, 250 mg twice daily. Child <5 years, 125 mg twice daily.
Tonsillitis or pharyngitis (presumed *S. pyogenes*), scarlet fever: Adult, child >10 years, 500 mg twice daily for 5 days (10 days to prevent rheumatic fever). Child <10 years, 250 mg twice daily for 5 days (10 days to prevent rheumatic fever).

**Administration instructions**

IV penicillins are physically incompatible with many substances (including aminoglycosides); give separately. Avoid rapid IV administration of large doses as it may result in seizures. Lignocaine can be used to reconstitute IM injections to reduce local pain.

**Practice points**

- Phenoxymethylpenicillin is less active than benzylpenicillin; generally reserve for situations where high tissue concentrations are not required, e.g. acute sore throat.
- Antibiotics are not indicated for mild tonsillitis in communities at low risk of rheumatic fever.
- For streptococcal infections in at-risk populations, give a 10-day course to ensure eradication of *S. pyogenes* from the nasopharynx and to reduce the risk of rheumatic fever.
- Food has little effect on absorption.
- Use frequent doses of penicillins for maximal antibacterial effect.
- Monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days).
- Avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven.

**Products**

- PHENOXYMETHYL PENCILLIN SUSP. 200-250 MG/5ML 60ML (ORVEK®, OSPEN®, VIKADAR®)
- PHENOXYMETHYL PENCILLIN TABS 250 MG (ORVEK®, OSPEN®)
- PHENOXYMETHYL PENCILLIN TABS 500 MG (ORVEK®, OSPEN®, VIKADAR®)

**Procaine Benzylpenicillin**

Beta-lactamase labile

**Mode of action**

Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

**Indications:** Respiratory tract infections (e.g. pneumococcal) in remote areas where compliance with oral treatment is unlikely, Syphilis, Cellulitis, erysipelas

**Treatment or prevention of infection caused by susceptible bacteria**

**Contraindications**

- Allergy to penicillins, Cefalosporins or carbapenems. Serious allergic reactions to procaine

**Specific considerations**

- Same as Benzathine Penicillin

**Adverse effects:**

- Same as Benzathine Penicillin

**Dosage**

Adult, IM, 1–1.5 g once daily. Maximum 4.5 g daily.
Child, IM, 50 mg/kg once daily.
Early syphilis (primary, secondary or latent <2 years duration), IM, 1 g daily for 10 days.
Late latent syphilis (in the absence of neurosyphilis), IM, 1 g daily for 15 days.
Dose equivalence: 1 g = 1 million units.

**Administration instructions**

- Give by deep IM injection only (do not give IV).
- Give doses >1.5 g (pack size) as 2 injections at separate sites.
- Lignocaine can be used to reconstitute IM injections to reduce local pain.

**Practice points**

- Absorbed slowly into circulation and hydrolysed to benzylpenicillin; use when prolonged, low concentrations of benzylpenicillin are appropriate and adequate.
- Benzathine penicillin preferred to treat syphilis (fewer doses).
- duration of effect is 12–24 hours.
- syringes are not graduated; part syringe dosing is not accurate but is used
- use frequent doses of penicillins for maximal antibacterial effect
- monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days)
- lignocaine can be used to reconstitute IM injections to reduce local pain
- avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven

Products
PROCAINE BENZYL PENICILLIN VIAL 400,000 IU/VIAL (FORTIPEN®)

5.01.01.02 Penicillinase-resistant penicillins

CLOxacillin
Mode of action: Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

Indications
Cloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Adverse Effects
Gastrointestinal effects such as diarrhoea and nausea, hypersensitivity, a sore mouth or tongue or a black hairy tongue. Pseudomembranous colitis. Other adverse effects have generally been associated with large intravenous doses of benzylpenicillin; patients with renal impairment are also at increased risk. These adverse effects include haemolytic anaemia and neutropenia, both of which might have some immunological basis; prolongation of bleeding time and defective platelet function; convulsions and other signs of CNS toxicity (encephalopathy has followed intrathecal administration and can be fatal); and electrolyte disturbances because of the large amounts of potassium or sodium given when benzylpenicillin potassium or sodium, respectively, are used. Hepatitis and cholestatic jaundice have been reported rarely with some penicillins, notably penicillinase-resistant penicillins. Anaphylactic reactions occur in about 0.05% of patients, usually after parenteral use, but they have also been reported after taking penicillin by mouth.

Dosage and route of administration
Cloxacillin is given by mouth as the sodium salt and doses are expressed in terms of the equivalent amount of cloxacillin. 1.09 g of cloxacillin sodium is approximately equivalent to 1 g of cloxacillin. It should be given at least 30 minutes before meals as the presence of food in the stomach reduces absorption. Usually oral doses are 250 to 500 mg four times daily. Children may be given 50 to 100 mg/kg daily in divided doses every 6 hours.

Cloxacillin sodium has also been given by intramuscular or slow intravenous injection or infusion. Other routes of administration have included intra-articular or intrapleural injection, and inhalation. Cloxacillin may be used with other antibacterials, including ampicillin, to produce a wider spectrum of activity.

Products
CLOXACILLIN CAPS 250 MG (CLOXADAR®, HIKMACLOX®, ULTRAXIN®)
CLOXACILLIN SUSP. 125 MG/5ML 100 ML BOTTLE (HIKMACLOX®)
CLOXACILLIN VIAL 500 MG/VIAL (MONOCLOX®, ULTRAXIN®)

5.01.01.03 Broad-spectrum penicillins

AMOXYCILLIN
Beta-lactamase labile

Mode of action
Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

Indications
Exacerbation of chronic bronchitis, community-acquired pneumonia, Acute bacterial otitis media, sinusitis, Gonococcal infection, Epididymo-orchitis, acute prostatitis, acute pyelonephritis, UTI, Non-surgical prophylaxis of endocarditis, Acute cholecystitis, peritonitis, eradication of H. pylori (with other agents)

Treatment or prevention of infection caused by susceptible bacteria

Contraindications
Allergy to penicillins, Cefalosporins or carbapenems
Specific considerations
Lymphoblastic leukaemia, HIV infection: increased risk of rash.
Renal impairment: Reduce dose in severe impairment.
Sodium restriction, cardiac failure: some parenteral penicillins, eg benzylpenicillin, piperacillin and ticarcillin with clavulanic acid, have high sodium content and in high doses can precipitate cardiac failure in patients with poor cardiac reserve.
Infectious mononucleosis: high incidence of rash, especially with ampicillin and amoxycillin.
Renal impairment: High parenteral doses and/or prolonged treatment may result in electrolyte disturbance and neurotoxicity (convulsions, coma), due to accumulation of the penicillin.
Pregnancy: considered safe to use; ADEC category A.
ADEC category B2: dicloxacillin, ticarcillin with clavulanic acid.
Breastfeeding: All penicillins considered safe; they may cause loose bowel actions in the infant.

Adverse effects
Penicillins are generally well tolerated.
Common: diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site (less common with benzylpenicillin), superinfection (including candidiasis) especially during prolonged treatment with broad spectrum penicillins, allergy.
Infrequent: fever, vomiting, erythema, exfoliative dermatitis, angioedema, pseudomembranous colitis
Rare: anaphylactic shock, bronchospasm, interstitial nephritis, serum sickness-like syndrome, blood dyscrasias including haemolytic anaemia, electrolyte disturbances, neurotoxicity, bleeding, haemolytic uraemic syndrome (high dose and/or renal impairment), nephropathy (with parenteral use), Stevens–Johnson syndrome, toxic epidermal necrolysis

Dosage
Adult
Oral, 250–500 mg every 8 hours or 1 g tablet twice a day.
IM/IV, 1 g every 6 hours. Maximum 12 g daily (eg to treat Listeria meningitis).
Neonate
IV, 25–50 mg/kg every 12 hours in first week of life, then every 8 hours in weeks 2–4. After the first week, may be given every 6 hours in severe infections.
Oral, 7.5–25 mg/kg every 8 hours.
Child
Oral, 7.5–25 mg/kg every 8 hours.
IM/IV, 10–25 mg/kg every 8 hours. Maximum 50 mg/kg every 4 hours.
Severe renal impairment
Adult, IM/IV, 1–2 g every 12–24 hours.
Prophylaxis of endocarditis
Dental and upper respiratory tract procedures
Adult, oral, 2 g single dose 1 hour before procedure.
Give 2 g IV just before procedure (or IM 30 minutes before procedure) if oral therapy not possible.
Child, oral, 50 mg/kg (maximum 2 g) single dose 1 hour before procedure.
Give 50 mg/kg (maximum 2 g) IV just before procedure (or IM 30 minutes before procedure) if oral therapy not possible.
Genitourinary and some GI procedures
Adult, IV, 2 g just before procedure (or IM 30 minutes before procedure). For high risk people add gentamicin and follow by 1 g oral/IV/IM amoxycillin 6 hours later.
Child, IV, 50 mg/kg (maximum 2 g) just before procedure (or IM 30 minutes before procedure). For high risk children add gentamicin and follow by 25 mg/kg amoxycillin (maximum 1 g) oral/IV/IM 6 hours later.
Gonococcal infection (confirmed non–beta-lactamase-producing N. gonorrhoeae)
Oral, 3 g single dose with probenecid. Add azithromycin single dose as presumptive treatment for Chlamydia if in a high risk group.
Eradication of H. pylori
With clarithromycin, oral, 1 g amoxycillin twice daily for 7 days.
With metronidazole, oral, 500 mg amoxycillin 3 times daily for 14 days.

Practice points
- injection contains 2.6 mmol (60 mg) sodium per gram
• use amoxycillin rather than ampicillin orally as it is better absorbed and given 3 times daily (rather than 4 times daily). However, it is probably better to use ampicillin to treat shigellosis as more antibiotic remains in the intestine
• IV amoxycillin is an alternative to IV ampicillin
• use frequent doses of penicillins for maximal antibacterial effect
• monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days)
• avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven

Products
AMOXYCILLIN CAPS 250 MG (AS TRIHYDRATE) (AMOXYDAR®, AMOXIL®, AMOXIPEN®, HICONCIL®, JULPHAMOX®, MOXEPHARM®, MOXIRAM®, OSPAMOX®, PENAMOX®, ULTRAMOX®)

AMOXYCILLIN CAPS 500 MG (AS TRIHYDRATE) (AMOXIL®, AMOXIBEL®, AMOXIPEN®, APROXAL®, AMOXYDAR®, HICONCIL®, HYMOX®, JULPHAMOX®, MOXEPHARM®, MOXILEN®, MOXIRAM®, OSPAMOX®, PENAMOX®, ULTRAMOX®)

AMOXYCILLIN SUSP. 250 MG/5ML (AS TRIHYDRATE) 100 ML BOTTLE (AMOXIL®, AMOXYDAR®, APROXAL®, HICONCIL®, HYMOX®, JULPHAMOX®, MOXILEN®, MOXIRAM®, OSPAMOX®, PENAMOX®, ULTRAMOX®)

AMOXYCILLIN WITH CLAVULANIC ACID

Mode of action
Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

Indications
Hospital-acquired pneumonia, Epididymo-orchitis (urinary tract source), UTI, Bites and clenched fist injuries, Otitis media (unresponsive to amoxycillin), Acute bacterial sinusitis (unresponsive to amoxycillin), Acute cholecystitis (after IV treatment), Melioidosis, Treatment or prevention of infection caused by susceptible bacteria

Contraindications
Allergy to penicillins, Cefalosporins or carbapenems.
Cholestatic jaundice or hepatic dysfunction associated with amoxycillin with clavulanic acid, or ticarcillin with clavulanic acid

Specific considerations
Lymphoblastic leukaemia, HIV infection: increased risk of rash.
Sodium restriction, heart failure: some parenteral penicillins, eg benzylpenicillin, piperacillin and ticarcillin with clavulanic acid, have high sodium content and in high doses can precipitate cardiac failure in patients with poor cardiac reserve.
Infectious mononucleosis: high incidence of rash, especially with ampicillin and amoxycillin.
Renal impairment: Reduce dose in moderate-to-severe impairment.
Hepatic impairment: Amoxycillin with clavulanic acid can cause cholestatic hepatitis. Pre-existing hepatic impairment is not a risk factor.
Elderly: Increased risk of hepatitis in people >55 years.
Pregnancy: Avoid in women with premature rupture of the membranes as there may be an increased risk of neonatal necrotising enterocolitis; ADEC category A
Breastfeeding: Considered safe; it may cause loose bowel actions in the infant.

Adverse Effects
Penicillins are generally well tolerated.
Common: transient increases in liver enzymes and bilirubin, diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site (less common with benzylpenicillin), superinfection (including candidiasis) especially during prolonged treatment with broad spectrum penicillins; allergy
Infrequent: fever, vomiting, erythema, exfoliative dermatitis, angioedema, pseudomembranous colitis
Rare: acute generalised exanthemeatous pustulosis, anaphylactic shock, bronchospasm, interstitial nephritis, serum sickness-like syndrome, electrolyte disturbances, neurotoxicity, bleeding, blood dyscrasias including haemolytic anaemia, haemolytic uraemic syndrome (high dose and/or renal impairment), nephropathy (with parenteral use), Stevens–Johnson syndrome, toxic epidermal necrolysis
Cholestatic hepatitis: Generally less severe than flucloxacillin hepatitis, and is usually reversible. Symptoms may
appear during, or several weeks after, treatment and may persist for 5–6 weeks. The risk increases with age (>55 years), male sex and length of treatment.

**Dosage**

Doses are based on amoxycillin component.

Adult: 500–875 mg every 12 hours for 5–10 days.

Child: 7.5–15 mg/kg every 8 hours for 5–10 days; can use up to 22.5 mg/kg every 8 hours in severe infections.

Acute bacterial sinusitis: Adult, 875 mg 3 times a day for 7–14 days. Child, 22.5 mg/kg 3 times a day for 7–14 days.

Urinary tract infection: Adult, 500 mg twice a day for 5 days (10 days if pregnant). Child, 12.5 mg/kg twice a day for 5 days.

Moderate-to-severe renal impairment

Moderate impairment: Adult, give normal initial dose then 250–500 mg every 12 hours.

Severe impairment: Adult, give normal initial dose then 250–500 mg every 24 hours.

**Patient counselling**

This medicine is absorbed best if taken with food.

**Practice points**

- similar activity to amoxycillin, but is also active against beta-lactamase–producing Gram-positive (S. aureus) and many Gram-negative organisms (Moraxella catarrhalis, H. influenzae, Proteus spp., E. coli, Klebsiella spp.) and Gram-negative anaerobes

- addition of metronidazole is not needed for Gram-negative anaerobic infections (e.g. Bacteroides spp.)

- monitor hepatic function if treatment lasts for >14 days, especially if there are other risk factors

- use frequent doses of penicillins for maximal antibacterial effect

- monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days)

- avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven

**Products**

AMOXYCILLIN + CLAVULANIC ACID SUSP. 125 MG (AS TRIHYDRATE)+31 MG (AS POTASSIUM SALT) MG/5ML 100 ML BOTTLE (AMOCLAN®, AUGMENTIN®, CLAVAR®, CURAM®, JULMENTIN®, KLAVOX®, MEGAMOX®, MOXICLAV®, RAMOCLAV®)

AMOXYCILLIN + CLAVULANIC ACID SUSP. 250 MG (AS TRIHYDRATE) 62.5 MG (AS POTASSIUM SALT) MG/5ML 100 ML BOTTLE (AMOCLAN®, AUGMENTIN®, CLAMOXIN®, CLAVAR®, CURAM®, JULMENTIN®, KLAVOX®, MEGAMOX®, MOXICLAV®, RAMOCLAV®)

AMOXYCILLIN + CLAVULANIC ACID TABS 250 MG (AS TRIHYDRATE)+125 MG (AS POTASSIUM SALT) (AMOCLAN®, AUGMENTIN®, CLAVAR®, KLAVOX®, MOXICLAV®, RAMOCLAV®, JULMENTIN®)

AMOXYCILLIN + CLAVULANIC ACID TABS 500 MG (AS TRIHYDRATE)+125 MG (AS POTASSIUM SALT) (AMOCLAN®, AUGMENTIN®, CLAVAR®, CLAVODAR®, CURAM®, JULMENTIN®, KLAVOX®, MOXICLAV®, RAMOCLAV®)

AMOXYCILLIN + CLAVULANIC ACID VIAL 600 MG [500 MG (AS SODIUM SALT)+100 MG (AS POTASSIUM SALT)]/VIAL (AMOCLAN®, AUGMENTIN®)

AMOXYCILLIN + CLAVULANIC ACID VIAL 1,200 MG [(1000 MG (AS SODIUM SALT)+200 MG (AS POTASSIUM SALT)] (AMOCLAN®, AUGMENTIN®)

**AMPICILLIN**

Beta-lactamase labile

**Mode of action**

Bactericidal; penicillins interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**

Same as amoxacillin

**Contraindications**

Allergy to penicillins, Cefalosporins or carbapenems

**Specific considerations**
Same as amoxacillin

**Adverse effects**
Same as amoxacillin

**Dosage**

**Adult:** Oral, 250–500 mg every 6 hours. Usual maximum 4 g daily. IM/IV, 500 mg – 1 g every 4–6 hours. Use 200 mg/kg/day in divided doses every 4–6 hours in meningitis or septicemia. Maximum 14 g daily.

**Child:** Oral, 7.5–25 mg/kg every 6 hours, up to 4 g daily. IM/IV, 10–25 mg/kg every 6 hours. Maximum 50 mg/kg every 4 hours.

**Severe renal impairment:** Adult, 1–2 g IM/IV every 12–24 hours.

**Shigellosis:** Adult, oral 1 g every 6 hours for 5 days. Child, oral 25 mg/kg (maximum 1 g) every 6 hours for 5 days.

**Patient counselling**
Take capsules on an empty stomach, at least half an hour before meals and at bedtime.

**Practice points**
- use amoxycillin rather than ampicillin orally as it is better absorbed and given 3 times daily (ampicillin must be given 4 times daily). However, it is probably better to use ampicillin to treat shigellosis as more antibiotic remains in the intestine
- vomiting and diarrhoea are more common with ampicillin than with amoxycillin
- IV amoxycillin is an alternative to IV ampicillin
- injection contains 2.7 mmol (62 mg) sodium per gram
- use frequent doses of penicillins for maximal antibacterial effect
- monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days)
- rapid IV administration of large doses may result in seizures
- lignocaine can be used to reconstitute IM injections to reduce local pain
- avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven

**Products**

AMPICILLIN SUSP. 250 MG/5ML 100 ML BOTTLE (AMPIDAR FORTE®, LIFEAMPI®, PENTREXYL®, ULTRACILLIN FORTE®, STANDACILLIN®)

AMPICILLIN VIAL 250 MG/VIAL (PAMECIL®, PENTREXYL®, ULTRACILLIN®)

AMPICILLIN VIAL 500 MG/VIAL (PAMECIL®, PENTREXYL®, ULTRACILLIN®, STANDACILLIN®)

AMPICILLIN VIAL 1 GM/VIAL (PAMECIL®, PENTREXYL®, ULTRACILLIN®, STANSACILLIN®)

**05.01.01.04 Antipseudomonal penicillins**

**Piperacillin + Tazobactam**

**Mode of action**
Bactericidal: penicillins interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**
Mixed (aerobic and anaerobic) infections, especially if P. aeruginosa is involved febrile neutropenia

**Contraindications**
Allergy to penicillins, Cefalosporins or carbapenems. Jaundice and/or hepatic dysfunction with piperacillin with tazobactam, ticarcillin with clavulanic acid, or amoxycillin with clavulanic acid

**Specific considerations**
Coagulation disorder increases risk of bleeding abnormalities.
Cystic fibrosis: Higher incidence of rash and drug fever.
Sodium restriction, cardiac failure: some parenteral penicillins, eg benzylpenicillin, piperacillin and ticarcillin with clavulanic acid, have high sodium content and in high doses can precipitate cardiac failure in patients with poor cardiac reserve.
Renal impairment: High parenteral doses and/or prolonged treatment may result in electrolyte disturbance and neurotoxicity (convulsions, coma), due to accumulation of the penicillin.
People with renal impairment are more likely to experience bleeding abnormalities; reduce dose in severe impairment.
Children: Indications in paediatric infections are not defined other than for serious intra-abdominal infections; use
only if other agents are not suitable.
Pregnancy: Considered safe to use; ADEC category B1.
Breastfeeding: Considered safe; it may cause loose bowel actions in the infant.

**Adverse effects**

Penicillins are generally well tolerated.
Common: diarrhea, nausea, rash, urticaria, pain and inflammation at injection site (less common with benzylpenicillin), superinfection (including candidiasis) especially during prolonged treatment with broad spectrum penicillins
Infrequent: fever, vomiting, erythema, exfoliative dermatitis, angioedema, pseudomembranous colitis
Rare: transient increases in liver enzymes and bilirubin (more common than with piperacillin alone), cholestatic jaundice, bleeding abnormalities (prolonged bleeding times and altered platelet aggregation) with high doses, hypokalaemia (high doses in people treated with cytotoxics, diuretics or who have hepatic disease), anaphylactic shock, bronchospasm, interstitial nephritis, serum sickness-like syndrome, blood dyscrasias, electrolyte disturbances, neurotoxicity, bleeding, haemolytic anaemia, haemolytic uraemic syndrome (high dose and/or renal impairment), nephropathy (with parenteral use), Stevens–Johnson syndrome, toxic epidermal necrolysis

**Dosage**

Doses are expressed as piperacillin component.
Adult, IV/IM, 2–4 g every 6–8 hours. Maximum 24 g daily.
Child, IV, 100 mg/kg every 6–8 hours.
Severe renal impairment: IV, 2–4 g every 12 hours.

**Practice points**

- reserve for mixed (aerobic and anaerobic) and Pseudomonas infections
- no role in Pseudomonas infections resistant to piperacillin as the resistance is not usually beta-lactamase–mediated
- often used with an aminoglycoside, e.g. for febrile neutropenia; in these circumstances, monitor renal function because of the increased risk of renal impairment; avoid aminoglycoside in severe renal impairment if possible
- similar antibacterial spectrum to ticarcillin with clavulanic acid but more active against some Gram-negative organisms and enterococci because of the greater intrinsic activity of piperacillin
- monitor serum potassium in those who are likely to develop hypokalaemia during treatment
- Contains 2.35 mmol (54 mg) sodium per gram piperacillin with 125 mg tazobactam
- may reconstitute with lignocaine 0.5% injection for IM administration; maximum 2 g at one site
- use frequent doses of penicillins for maximal antibacterial effect
- IV penicillins are physically incompatible with many substances (including aminoglycosides); give separately
- monitor renal and hepatic function, and complete blood picture during prolonged high dose treatment (>10 days)
- rapid IV administration of large doses may result in seizures
- lignocaine can be used to reconstitute IM injections to reduce local pain
- avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven

**Products**

PIPERACILLIN+TAZOBACTAM VIAL 4+0.5 GM/VIAL (TAZOCIN®)

**05.01.02 Cefalosporins, cefamycins, and other beta-lactams**

**CEFALOSPORINS**

The cefalosporins are broad-spectrum antibiotics used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. The pharmacology of the cefalosporins is similar to that of the penicillins, excretion being principally renal. Cefalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed; cefotaxime is a suitable cefalosporin for infections of the CNS (e.g meningitis). The principal side-effect of the cefalosporins is hypersensitivity and about 10% of penicillin-sensitive patients will also be allergic to the cefalosporins.

Cefradine (cephradine) has generally been replaced by the newer cefalosporins.

Cefuroxime is a ‘second generation’ cefalosporin that is less susceptible than the earlier cefalosporins to inactivation by beta-lactamases. It is, therefore, active against certain bacteria which are resistant to other drugs and has greater activity against Haemophilus influenzae and Neisseria gonorrhoeae.
Cefotaxime, ceftazidime and ceftriaxone are ‘third generation' cefalosporins with greater activity against certain Gram-negative bacteria than the ‘second generation' cefalosporins. However, they are less active than cefuroxime against Gram-positive bacteria, most notably Staphylococcus aureus. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

Ceftazidime has good activity against pseudomonas. It is also active against other Gram-negative bacteria. Ceftriaxone has a longer half-life and is therefore given only once daily. Indications include serious infections such as septicaemia, pneumonia, and meningitis. The calcium salt of ceftriaxone forms a precipitate in the gall bladder which may rarely cause symptoms but these usually resolve when the antibiotic is stopped.

**Orally active cefalosporins**
The orally active ‘first generation' cefalosporins, cefalexin, cefradine, and cefadroxil and the ‘second generation' cefalosporins, cefaclor and cefprozil, have a similar antibacterial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy, respiratory-tract infections, otitis media, sinusitis, and skin and soft-tissue infections. Cefaclor has good activity against H. influenzae, but it is associated with protracted skin reactions especially in children. Cefadroxil has a long duration of action and can be given twice daily; it has poor activity against H. influenzae. Cefuroxime axetil, an ester of the ‘second generation' cefalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed.

Cefixime has a longer duration of action than the other cefalosporins that are active by mouth. It is only licensed for acute infections.

Cefpodoxime proxetil is more active than the other oral cefalosporins against respiratory bacterial pathogens and it is licensed for upper and lower respiratory-tract infections.

**Oral infections**
The cefalosporins offer little advantage over the penicillins in dental infections, often being less active against anaerobes. Infections due to oral streptococci (often termed viridans streptococci) which become resistant to penicillin are usually also resistant to cefalosporins. This is of importance in the case of patients who have had rheumatic fever and are on long-term penicillin therapy. Cefalexin and cefradine have been used in the treatment of oral infections.

### 05.01.02.01 First generation cefalosporins

**CEFALEXIN**

**Mode of action**
Interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**
Staphylococcal and streptococcal infections in people with mild-to-moderate penicillin allergy, UTIs due to susceptible Gram-negative bacteria, Epididymo-orchitis (urinary tract source)

**Contraindications**
Allergy to penicillins, Cefalosporins or carbapenems.

**Specific considerations**
Impaired vitamin K synthesis, low vitamin K stores (chronic disease and malnutrition): increased risk of bleeding with all cefalosporins, especially cephazolin, cephamandole and ceftriaxone; monitor INR; consider use of vitamin K for prophylaxis or treatment.

Sodium restriction: some parenteral cefalosporins have high sodium content.

Renal impairment: In severe impairment there is an increased risk of neurotoxicity (convulsions or coma) with high doses. Reduce dose in severe impairment.

Pregnancy: Considered safe to use; ADEC category A.

Breastfeeding: May cause loose bowel actions in the infant; considered safe to use.

**Adverse effects**
Common: diarrhoea, nausea, rash, electrolyte disturbances, pain and inflammation at injection site
Infrequent: vomiting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, drug fever
Rare: cholestatic hepatitis, anaphylactic shock, bronchial obstruction, urticaria, angioedema, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness–like syndrome (infrequent with cefaclor), neurotoxicity (including seizures), blood dyscrasias, eg neutropenia, thrombocytopenia, bleeding, haemolytic anaemia, renal impairment

**Dosage**
Adult, 250–500 mg every 6 hours or 500 mg – 1 g every 6–12 hours. Maximum 4 g daily; if higher doses required consider parenteral therapy.
Child, 6.25–12.5 mg/kg every 6 hours. Maximum 25 mg/kg/dose.
Severe renal impairment: Adult, 250–500 mg every 8–12 hours; higher doses are often used.
Prophylaxis UTI: Adult, 250 mg at night. Child, 12.5 mg/kg (maximum 250 mg) at night.
Uncomplicated UTI: 500 mg every 12 hours for 5 days.

Practice points

- give twice daily for uncomplicated UTIs, streptococcal pharyngitis and tonsillitis, skin and soft tissue infections; twice daily dosing is not recommended if >500 mg per dose is required
- monitor renal function and complete blood picture during prolonged (>10 days) and/or high dose treatment
- superinfection (including Candida and Enterococcus spp.) may occur, especially with use of broader spectrum cefalosporins and during prolonged treatment
- some enteric Gram-negative organisms (ESCAPP) naturally produce cefalosporinases; these enzymes may be induced and result in the emergence of resistance to broad spectrum drugs during treatment
- avoid penicillins and cefalosporins when the presence of ESCAPP organisms is suspected or proven
- some bacteria, including species of Klebsiella, Enterobacter and occasionally E. coli, have acquired the ability to produce extended spectra beta-lactamases (ESBLs) which confer resistance to all cefalosporins
- broad spectrum antibiotics, particularly third generation cefalosporins, are an independent risk factor for vancomycin-resistant enterococci (VRE) colonisation; their use should be restricted wherever possible

Products

**CEFALEXIN CAPS 250 MG (AS MONOHYDRATE)** (CEPHACENT®, CEPHADAR®, FELEXIN®, KEFLEX®, LEXIN®, MEDOLEXIN®, MIDAFLEX®, PHARMEXIN®, RAMOXIN®, ULTRASPORIN®, UNILEXIN®)

**CEFALEXIN CAPS 500 MG (AS MONOHYDRATE)** (BELACEF FORTE®, CEFRIN®, CEPHADAR FORTE®, CEPHALEX®, FELEXIN®, KEFLEX®, LEXIN®, MEDOLEXIN®, MIDAFLEX®, OSPEXIN®, PHARMEXIN®, RAMOXIN®, ULTRASPORIN®, UNILEXIN®)

**CEFALEXIN SUSP. 250 MG/5ML (AS MONOHYDRATE)** 100 ML BOTTLE (CEPHADAR®, CEPHALEX®, FELEXIN®, LEXIN®, KEFLEX®, MEDOLEXIN®, MIDAFLEX®, OSPEXIN®, PHARMEXIN®, RAMOXIN®, ULTRASPORIN®, UNILEXIN®)

**CEFAZOLIN**

Mode of action
Interfere with bacterial cell wall peptidoglycan synthesis.

Indications
Staphylococcal and streptococcal infections in people with mild-to-moderate penicillin allergy
Surgical prophylaxis
UTIs due to susceptible Gram-negative bacteria

Contraindications
Allergy to penicillins, cefalosporins or carbapenems

Specific considerations.
Same as Cefalexin

Adverse effects
Rare
confusion (after large doses in renal failure)
Other effects: Same as Cefalexin

Dosage
Adult, IM/IV, 0.5–1 g every 6–8 hours. Usual maximum 6 g daily (up to 12 g daily has been used).
Child, IM/IV, 10–15 mg/kg every 8 hours. Severe infections, 25–37.5 mg/kg every 6 hours.
Renal impairment: Moderate, IM/IV, 0.5–1 g every 12 hours. Severe, IM/IV, 0.5–1 g every 24 hours.
Surgical prophylaxis: Adult, IV, 1 g at induction of anaesthesia. Child, IV, 25 mg/kg (maximum 1 g) at induction of anaesthesia.

Practice points
- dosing every 8 hours may offer cost benefit over cefalothin
- monitor renal function and complete blood picture during prolonged (>10 days) and/or high dose treatment
• IV preparations are physically incompatible with many substances; avoid mixing with other drugs
• rapid IV administration of large doses may result in seizures, especially if inappropriately high doses are used in renal impairment
• superinfection (including Candida and Enterococcus spp.) may occur, especially with use of broader spectrum cefalosporins and during prolonged treatment
• some enteric Gram-negative organisms (ESCAPP) naturally produce cefalosporinases; these enzymes may be induced and result in the emergence of resistance to broad spectrum drugs during treatment
• avoid penicillins and cefalosporins when the presence of ESCAPP organisms is suspected or proven
• some bacteria, including species of Klebsiella, Enterobacter and occasionally E. coli, have acquired the ability to produce extended spectrum beta-lactamases (ESBLs) which confer resistance to all cefalosporins
• broad spectrum antibiotics, particularly third generation cefalosporins, are an independent risk factor for vancomycin-resistant enterococci (VRE) colonisation; their use should be restricted wherever possible

Products
CEFAZOLIN SODIUM VIAL 500 MG/VIAL (CEFAZOLIN®, HIKMA CEFAZOLIN®)
CEFAZOLIN SODIUM VIAL 1GM/VIAL (CEFAZOLINE®, HIKMA CEFAZOLINE®, REFLIN®, ZOLECEF®)

05.01.02.01 Second generation cefalosporins

CEFOXITIN
Mode of action
Interfere with bacterial cell wall peptidoglycan synthesis.
Indications
Alternative to other antimicrobial combinations for surgical prophylaxis for some GI procedures
Alternative to other antimicrobial combinations for mixed anaerobic infections, e.g. peritonitis
Contraindications
Allergy to penicillins, cefalosporins or carbapenems
Specific considerations
Same as Cefalexin
Adverse effects
Same as Cefalexin
Dosage
Adult, IV/IM, 1–2 g every 8 hours. Maximum 12 g daily.
Child, IV/IM, 20–40 mg/kg every 8 hours.
Severe infections: Adult, IV/IM, 2–3 g every 6–8 hours; or 2 g every 4 hours. Child, IV/IM, 40 mg/kg every 6 hours.
Surgical prophylaxis: Adult, IV, 2 g at induction of anaesthesia.
Renal impairment, adult: Moderate, IV/IM, 1–2 g every 12–24 hours. Severe, IV/IM, 1–2 g initially then 0.5–1 g every 12–24 hours.
Practice points
Same as Cefalexin
Products
CEFOXITIN SODIUM VIAL 1 GM/VIAL IM OR IV (FOXITIN®, MEFOXIN®, VOXITIN®, ZOXIN®)

CEFUROXIME
Mode of action
Interfere with bacterial cell wall peptidoglycan synthesis.
Indications
Acute bacterial sinusitis, Respiratory tract infections caused by H. influenzae, Otitis media, Gonococcal infections (alternative to amoxycillin)
Contraindications
Allergy to penicillins, cefalosporins or carbapenems
Specific considerations
Same as Cefalexin
Adverse effects
Same as Cefalexin
Dosage
Adult, 250–500 mg every 12 hours.
Severe renal impairment: Adult, 250–500 mg every 24 hours.
Gonococcal infection: Adult, 1 g single dose.

Patient counselling
Cefuroxime is absorbed best if you take it with a light meal.

Practice points
- may be used in penicillin allergy (unless severe or immediate)
- Other points: Same as Cefalexin

Products
CEFUXORXIME SUSP. 125 MG/5ML (AS AXETIL) 50 ML BOTTLE (FROXIME®, ORAXIM®, U-CEF®, ZINNAT®)

CEFUXORXIME TABS 500 MG (AS AXETIL) (AXENATE®, CEFUREX®, CEFUTIL®, FROXIME®, ORAXIM®, U-CEF®, ZINNAT®, ZINAXIM®)

CEFUXORXIME VIAL 750 MG/VIAL (AS SODIUM) (AXETINE®, CEFUTIL®, FUROCEF®, GONIF®, MAXIL®, NIZACEF®, SUPERO®, ZILISTEN®, ZINACEF®, ZINOXIME®)

CEFUXORXIME VIAL 1.5 GM/VIAL (AS SODIUM) (AXETINE®, CEFUTIL®, MAXIL®, NIZACEF®, ZILISTEN®, ZINACEF®, ZINOXIME®)

05.01.02.03 Third generation cefalosporins

CEFIXIME

Mode of action
Interferes with bacterial cell wall peptidoglycan synthesis

Indications
Treatment of acute infections caused by susceptible organisms including gonorrhoea, otitis media, pharyngitis, lower respiratory-tract infections such as bronchitis, and urinary-tract infections.

Contra-indications
Allergy to penicillins, Cefalosporins or carbapenems

Specific considerations ;
Same as Cephalexin

Adverse Effects
Gastrointestinal disturbances, especially diarrhoea, hypoprothrombinaemia, increases in prothrombin times, antibiotic-associated colitis, and hypersensitivity reactions, including skin rashes, urticaria, eosinophilia, fever, reactions resembling serum sickness, and anaphylaxis. There may be a positive response to the Coombs' test although haemolytic anaemia rarely occurs. Neutropenia and thrombocytopenia have occasionally been reported. Agranulocytosis has been associated rarely with some cefalosporins. Bleeding complications related to hypoprothrombinaemia and/or platelet dysfunction have occurred.

Dosage
Cefixime is available as the trihydrate and doses are expressed in terms of anhydrous cefixime. It is given by mouth in adult doses of 200 to 400 mg daily as a single dose or in two divided doses. Children over 6 months and under 50 kg may be given 8 mg/kg daily as an oral suspension, again as a single dose or in two divided doses. For details of reduced dosage of cefixime in patients with moderate to severe renal impairment.

For uncomplicated gonorrhoea, a single oral dose of 400 mg is given.

Patient counselling
Care should be exercised in patients receiving anticoagulants and cefixime due to the possibility that cefixime may increase prothrombin times.

Practice Point :
Doses of cefixime should be reduced in patients with moderate to severe renal impairment. A dose of 200 mg daily should not be exceeded in patients with a creatinine clearance of less than 20 mL/minute.
**Products**
CEFIXIME CAPS 200 MG (BETIXIM®, CEFIX®, MAGNACEF®, SUPRAX®)
CEFIXIME SUSP. 100 MG/5ML  60 ML BOTTLE (BETIXIM®, CEFIX®, MAGNACEF®, SUPRAX®)

**CEFOTAXIME**

**Mode of action**
Interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**

**Contraindications**
Allergy to penicillins, cefalosporins or carbapenems.

**Specific considerations**
Same as Cephalexin.

**Adverse effects**
Common: diarrhoea, nausea, rash, electrolyte disturbances, pain and inflammation at injection site.
Infrequent: miting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, drug fever.
Rare: life-threatening arrhythmias with rapid IV administration, anaphylactic shock, bronchial obstruction, urticaria, angioedema, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness-like syndrome (infrequent with cefaclor), neurotoxicity (including seizures), blood dyscrasias, eg neutropenia, thrombocytopenia, bleeding, haemolytic anaemia, renal impairment.

**Dosage**
Adult, IV, 1–2 g every 8–12 hours. Maximum 12 g daily.
Child, IV, 25–50 mg/kg every 8 hours.
Bacterial meningitis, orbital cellulites: Adult, IV, 2 g every 6 hours. Child, IV, 50 mg/kg every 6 hours.
Severe renal impairment: Adult, IV, 1 g every 24 hours.

**Administration instructions**
Inject IV over 3–5 minutes to avoid rare arrhythmias.
Can be given IM but avoid doing so as it is painful.
IV preparations are physically incompatible with many substances; avoid mixing with other drugs.

**Practice points**
- Use in penicillin allergy (unless severe or immediate) and where aminoglycosides are contraindicated.
- Use instead of ceftriaxone for Gram-negative septicaemia in neonates because of better defined pharmacokinetics.
- A drug of choice (alternative to ceftriaxone) for the empirical treatment of bacterial meningitis (often with benzylpenicillin) and meningitis caused by H. influenzae (unless ampicillin sensitivity confirmed).
- Monitor renal function and complete blood picture during prolonged (>10 days) and/or high dose treatment.
- IV preparations are physically incompatible with many substances; avoid mixing with other drugs.
- Rapid IV administration of large doses may result in seizures, especially if inappropriately high doses are used in renal impairment.
- Superinfection (including Candida and Enterococcus spp.) may occur, especially with use of broader spectrum cefalosporins and during prolonged treatment.
- Some enteric Gram-negative organisms (ESCAPPM) naturally produce cefalosporinases; these enzymes may be induced and result in the emergence of resistance to broad spectrum drugs during treatment.
- Avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven.
- Some bacteria, including species of Klebsiella, Enterobacter and occasionally E. coli, have acquired the ability to produce extended spectrum beta-lactamases (ESBLs) which confer resistance to all cefalosporins.
- Broad spectrum antibiotics, particularly third generation cefalosporins, are an independent risk factor for vancomycin-resistant enterococci (VRE) colonisation; their use should be restricted wherever possible.
CEFTAXIME
Mode of action
Interfere with bacterial cell wall peptidoglycan synthesis.
Indications
Reserved for the treatment of P. aeruginosa infections. Melioidosis. Empirical treatment of sepsis in neutropenic or otherwise immunocompromised people
Contraindications
Same as Cephalexin
Specific considerations
Same as Cephalexin
Adverse effects
Same as Cephalexin
Dosage
Adult, IM/IV, 1–2 g every 8–12 hours.
Child, IM/IV, 25 mg/kg every 8 hours.
Life-threatening infections: Adult, 2 g IV every 8 hours. Child, 50 mg/kg IM/IV every 8 hours.
Cystic fibrosis: 50 mg/kg (maximum 2 g/dose) IV every 8 hours. 9 g daily has been used.
Melioidosis: Adult, 2 g IV every 6 hours. Child, 50 mg/kg IM/IV every 6 hours.
Use with either doxycycline or trimethoprim with sulfamethoxazole; treat for at least 2 weeks.
Renal impairment: Moderate, 1 g IM/IV every 24 hours. Severe, 1 g IM/IV, initial dose 1 g then 0.5 g IM/IV every 24 hours or 1 g every 48 hours.
Administration instructions
IV preparations are physically incompatible with many substances; avoid mixing with other drugs.
Practice points
- carbon dioxide is released during reconstitution; a gas relief needle may be needed to relieve positive pressure
- monitor renal function and complete blood picture during prolonged (>10 days) and/or high dose treatment
- rapid IV administration of large doses may result in seizures, especially if inappropriately high doses are used in renal impairment
- superinfection (including Candida and Enterococcus spp.) may occur, especially with use of broader spectrum cefalosporins and during prolonged treatment
- unless using cefoxitin give an additional antibiotic if anaerobic cover required in surgical prophylaxis
- some enteric Gram-negative organisms (ESCAPPM) naturally produce cefalosporinases; these enzymes may be induced and result in the emergence of resistance to broad spectrum drugs during treatment
- avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven
- some bacteria, including species of Klebsiella, Enterobacter and occasionally E. coli, have acquired the ability to produce extended spectrum beta-lactamases (ESBLs) which confer resistance to all cefalosporins
- broad spectrum antibiotics, particularly third generation cefalosporins, are an independent risk factor for vancomycin-resistant enterococci (VRE) colonisation; their use should be restricted wherever possible

Products
CEFOTAXIME SODIUM VIAL 500 MG/VIAL IM OR IV (CLAFORAN®, CEFTAX®, CLAFOTAX®, TAXIME®, TRIOTAX®)
CEFOTAXIME SODIUM VIAL 1 GM/VIAL IM OR IV (CEFOXIME®, CLAFORAN®, CEFTAX®, CLAFOTAX®, NASPOR®, SEFOTAK®, TRIOTAX®, UNITAX®, TAXIME®)

CEFTAZIDIME
Mode of action
Interfere with bacterial cell wall peptidoglycan synthesis.
Indications:
Same as Cefotaxime
Contraindications

CEFTIZOXIME
Mode of action
Interfere with bacterial cell wall peptidoglycan synthesis.
Indications:
Same as Cefotaxime
Contraindications:

Products
CEFTAZIDIME VIAL 1 GM/VIAL IM OR IV (CEFTUM®, FORTUM®, LEMOXOL®, ZIDIME®)
Same as Cefotaxime
Specific considerations
Same as Cefotaxime
Adverse Effects and Precautions
Same as Cefotaxime.
Dosage
Adult
IM/IV 1 to 2 g every 8 to 12 hours. In severe infections 2 to 4 g may be given intravenously every 8 hours; doses up to 2 g every 4 hours have been given in life-threatening infections.
Children > 6 months
50 mg/kg every 6 to 8 hours.
Uncomplicated urinary-tract infections: 500 mg every 12 hours is used.
Gonorrhoea: a single dose of 1 g
Renal impairment.
Doses of ceftizoxime should be modified in renal impairment; after a loading dose of 0.5 to 1 g, the maintenance dosage should be adjusted according to the patient's creatinine clearance (CC) and the severity of the infection:
CC 50 to 79 mL/minute: 0.5 to 1.5 g every 8 hours
CC 5 to 49 mL/minute: 0.25 to 1 g every 12 hours
CC less than 5 mL/minute: 250 to 500 mg every 24 hours or 0.5 to 1 g every 48 hours, after dialysis.
Patient counselling
It is given as the sodium salt by deep intramuscular injection, or intravenously as a slow injection over 3 to 5 minutes or as a continuous or intermittent infusion.
If 2 g of ceftizoxime is injected intramuscularly the dose should be divided between sites.
Doses are expressed in terms of the equivalent amount of ceftizoxime. 1.06 g of ceftizoxime sodium is approximately equivalent to 1 g of ceftizoxime.
Practice points
Same as Cefotaxime.
Products
CEFTIZOXIME SODIUM VIAL 1 GM/VIAL IM OR IV (CEFIZOX®)

CEFTRIAXONE
Mode of action
Interfere with bacterial cell wall peptidoglycan synthesis.
Indications
Empirical treatment of severe pneumonia (with other antimicrobials)
Empirical treatment of orbital cellulitis (sometimes with other antimicrobials)
Empirical treatment of bacterial meningitis (with other antimicrobials)
Gonococcal infection. , Pelvic inflammatory disease., Epiglottitis, Septicaemia
Prophylaxis of meningococcal meningitis (if rifampicin or ciprofloxacin contraindicated)
Prophylaxis of H. influenzae meningitis (if rifampicin is contraindicated)
Acute cholecystitis (alternative to ampicillin with gentamicin)
Acute peritonitis (with metronidazole)
Severe Salmonella enteritis (if other antibiotics unsuitable), typhoid, paratyphoid ( enteric fever)
Sexually acquired epididymo-orchitis (with doxycycline)
Contraindications
Allergy to penicillins, cefalosporins or carbapenems
Specific considerations
Same as Cephalaxin
In addition; Neonates and preterm infants—displaces bilirubin from albumin; may increase risk of bilirubin encephalopathy; cefotaxime is preferred to ceftriaxone for Gram-negative septicaemia in neonates.
Adverse effects
pancreatitis, cholecystitis, pseudolithiasis, nephrolithiasis
Pseudolithiasis, nephrolithiasis
Pseudolithiasis—dose-dependent, asymptomatic and reversible biliary sludge formation due to calcium–ceftiraxone complex; has been mistaken for gallstones on ultrasound scans and usually resolves after stopping treatment.
Nephrolithiasis—formation of calcium–ceftiraxone renal stones, sometimes requiring treatment; usually reversible.
Common: diarrhoea, nausea, rash, electrolyte disturbances, pain and inflammation at injection site
Infrequent: vomiting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, drug fever
Rare: anaphylactic shock, bronchial obstruction, urticaria, angioedema, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness-like syndrome which is infrequent with cefaclor, neurotoxicity (including seizures), blood dyscrasias, eg neutropenia, thrombocytopenia, bleeding, haemolytic anaemia, renal impairment

**Dosage**

**Adult, IM/IV, 1–2 g once daily (or in 2 divided doses). Maximum 4 g daily.**
Child, IM/IV, 50 mg/kg once daily.

**Bacterial meningitis: Adult, IV, 1–2 g every 12 hours. Child, IM/IV, 100 mg/kg once daily or 50 mg/kg every 12 hours.**

**Orbital cellulites: Adult, IV, 2 g once daily. Child, 50 mg/kg once daily.**

**Prophylaxis of meningococcal meningitis (rifampicin or ciprofloxacin contraindicated): Adult, IM, 250 mg as a single dose. Child, IM, 125 mg as a single dose.**

**Prophylaxis of H. influenzae meningitis (rifampicin contraindicated): Adult, IM, 1 g daily for 2 days. Child, IM, 50 mg/kg (maximum 1 g) daily for 2 days.**

**Uncomplicated gonococcal infection (beta-lactamase producing N. gonorrhoeae): Adult, IM, 250 mg as a single dose. Add doxycycline or azithromycin (presumptive treatments for Chlamydia and other non-gonococcal infections) if in high risk group.**

**Administration instructions**

IV preparations are physically incompatible with many substances; avoid mixing with other drugs.

**Practice points**

- use in penicillin allergy (unless severe or immediate) and where aminoglycosides are contraindicated
- a drug of choice (alternative to cefotaxime) for the empirical treatment of bacterial meningitis (with benzylpenicillin) and meningitis caused by *H. influenzae* (unless sensitivity to ampicillin confirmed)
- it may be more convenient to use than cefotaxime (less frequent dosing); may be used for outpatient IV treatment

**Products**

**CEFTRIAXONE SODIUM VIAL 500 MG/VIAL IM OR IV (AXONE®, LONGACEF®, MEGION®, ROXCEF®, SAMIXON®, ROCEPHIN®)**

**CEFTRIAXONE SODIUM VIAL 1 GM/VIAL IM OR IV (AXONE®, LONGACEF®, MEGION®, NOVOSEF®, OFRAMAX®, ROCEPHIN®, ROXCEF®, TRIAXONE®, VERACOL®, SAMIXON®)**

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**CEFEPIME**

**Mode of action**

Interfere with bacterial cell wall peptidoglycan synthesis.

**Indications**

*P. aeruginosa* infections, Empirical treatment of sepsis in neutropenic or otherwise immunosuppressed people, Infections caused by organisms resistant to other Cefalosporins

**Contraindications**

Same as Cephalexin

**Specific considerations**

Same as Cephalexin

**Adverse effects**

Same as Cephalexin

**Dosage**

Adult, child >12 years, IM/IV, 1–2 g every 12 hours. Maximum 6 g daily.
Child >2 months, IM/IV, 50 mg/kg every 12 hours.

**Life-threatening infections: Adult, child >12 years, IV, 2 g every 8–12 hours. Child >2 months, IM/IV, 50 mg/kg every 8 hours.**

Renal impairment: Give normal initial dose then:
Adult, child >12 years, Mild, IM/IV, 0.5 g every 24 hours to 2 g every 12 hours. Moderate, IM/IV, 0.5–2 g every 24 hours. Severe, IM/IV, 0.25–1 g every 24 hours.
Child >2 months: Mild, IM/IV, 12.5–50 mg/kg every 12–24 hours. Moderate, IM/IV, 12.5–50 mg/kg every 24 hours. Severe, IM/IV, 6.25–25 mg/kg every 24 hours.

Administration instructions
IV preparations are physically incompatible with many substances; avoid mixing with other drugs.

Practice points
• reserve for use in infections caused by multi-resistant organisms, e.g. P. aeruginosa, and for empirical treatment of sepsis in patients with neutropenia
• suitable as monotherapy for selected patients with febrile neutropenia
• some bacteria, including species of Klebsiella, Enterobacter and E. coli, have acquired the ability to produce extended spectrum beta-lactamases (ESBLs); stability of cefepime to ESBLs has not been established in vivo
• monitor renal function and complete blood picture during prolonged (>10 days) and/or high dose treatment
• IV preparations are physically incompatible with many substances; avoid mixing with other drugs
• rapid IV administration of large doses may result in seizures, especially if inappropriately high doses are used in renal impairment
• superinfection (including Candida and Enterococcus spp.) may occur, especially with use of broader spectrum cefalosporins and during prolonged treatment
• use an additional antibiotic for anaerobic cover (if required) in surgical prophylaxis (except with cefoxitin)
• some enteric Gram-negative organisms (ESCAPPM) naturally produce cefalosporinases; these enzymes may be induced and result in the emergence of resistance to broad spectrum drugs during treatment
• avoid penicillins and cefalosporins when the presence of ESCAPPM organisms is suspected or proven
• some bacteria, including species of Klebsiella, Enterobacter and occasionally E. coli, have acquired the ability to produce extended spectrum beta-lactamases (ESBLs) which confer resistance to all cefalosporins
• broad spectrum antibiotics, particularly third generation cefalosporins, are an independent risk factor for vancomycin-resistant enterococci (VRE) colonisation; their use should be restricted wherever possible

Products
CEFEPIME VIAL 0.5 GM/VIAL (AS HCL) 15 ML VIAL (MAXIPIME®)
CEFEPIME VIAL 1 GM/VIAL (AS HCL) 15 ML VIAL (MAXIPIME®)

05.01.02.05 Other beta-lactam antibiotics

AZTREONAM
Monobactam
Mode of action
Bactericidal; inhibits bacterial cell wall synthesis.
Indications
Infections caused by Gram-negative aerobes, e.g. septicaemia, lower respiratory tract infections in cystic fibrosis, in cases of allergy to other agents (e.g. severe penicillin allergy including anaphylaxis), or when other agents are ineffective
Contraindications
Serious allergic reaction to aztreonam
Specific considerations
Anticoagulated patients: Aztreonam may increase bleeding time; use with caution; monitor INR and APTT.
Penicillin- or cefalosporin-hypersensitivity: low risk of allergy to aztreonam in people who are allergic to penicillins and/or Cefalosporins; use with caution.
Renal impairment: Reduce dose in moderate-to-severe impairment.
Pregnancy: Safe to use; ADEC category B1.
Breastfeeding: Safe to use; may cause loose bowel actions in infant.
Adverse effects
Common: rash, diarrhoea, nausea, vomiting, abnormal taste, transient increases in liver transaminases, eosinophilia, phlebitis or thrombophlebitis at injection site
Infrequent: headache, dizziness, GI bleeding, abdominal cramps and bloating, oral ulceration
Rare: anaphylaxis, angioedema, bronchospasm, shock, pseudomembranous colitis, significant increases in liver
transaminases, hepatitis, jaundice, neutropenia, thrombocytopenia, prolonged bleeding time

**Dosage**

Doses given every 8 hours are usually adequate.

- **Adult, IM/IV**, 1–2 g every 6–8 hours.
- **Child, IM/IV**, 30 mg/kg every 8 hours.
- **Severe infections**: Adult, IV, 2 g every 6–8 hours. Child, IV, 50 mg/kg every 6–8 hours.
- **Complicated UTIs**, including pyelonephritis: Adult, IM/IV, 1 g every 8–12 hours.
- **Cystic fibrosis**: IM/IV, 50 mg/kg every 6–8 hours.
- **Maximum 8 g IV daily**.

**Renal impairment**: Moderate, IM/IV, initially 1–2 g, then 0.5–1 g every 8–12 hours. Severe, IM/IV, initially 1–2 g, then 0.25–0.5 g every 8–12 hours.

**Practice points**

- active against Gram-negative aerobic organisms, eg Enterobacteriaceae, P. aeruginosa (Gram-positive organisms and anaerobes are resistant)
- used to treat serious Gram-negative aerobic infections, eg as an alternative to aminoglycosides and broad spectrum (anti-pseudomonal) cefalosporins
- for empirical treatment of infection combine with other agents to cover anaerobic and/or Gram-positive infections
- less toxic than aminoglycosides
- use with an aminoglycoside to treat serious P. aeruginosa infections
- aztreonam is more stable than cefalosporins to inducible Amp C beta-lactamases produced by some enteric Gram-negative organisms (ESCAPPM but, like all cefalosporins, is susceptible to extended spectrum beta-lactamases (ESBLs) produced by some strains of Klebsiella, E. coli and Enterobacter spp.

**Products**

AZTREONAM VIAL  500 MG/VIAL (AZACTAM®)

**IMIPENEM**

**Mode of action**

Inhibit bacterial cell wall synthesis; usually bactericidal; resistant to most beta-lactamases.

**Indications**

Empirical treatment of nosocomial infections and life-threatening infections (when other antibacterials are inappropriate or contraindicated), or when multi-resistant Gram-negative infections are suspected or proven

Empirical treatment of febrile neutropenic patients

Treatment of severe mixed aerobic and anaerobic infections, particularly when combinations with an aminoglycoside are contraindicated, Melioidosis (with other agents)

**Contraindications**

Meningitis, Serious allergic reaction to a carbapenem

**Specific considerations**

Allergy to penicillins, cefalosporins or carbapenem.

Neutropenia: drug-related nausea and vomiting are more likely to occur.

CNS disorders (eg history of seizures): increased risk of neurotoxicity (use meropenem).

Treatment with ganciclovir or valganciclovir: increased risk of seizures; avoid combinations.

Renal impairment: Reduce dose. There is an increased risk of neurotoxicity; use with caution. Use only if no suitable alternative in severe impairment.

Pregnancy: Contact one of the specialized information centres; ADEC category B3.

Breastfeeding: safe to use; may cause loose bowel actions in infant.

**Adverse effects**

Common: nausea, vomiting, diarrhoea, local injection site reactions, eg phlebitis

Infrequent: fever, dizziness, somnolence, confusion, tremor, paraesthesia, headache, psychiatric disturbances, pseudomembranous colitis, encephalopathy, seizures, hypotension, positive Coombs’ test, increases in liver function tests, raised urea and creatinine

Rare: hepatitis, erythema multiforme, Stevens–Johnson syndrome, angioedema, tachycardia, renal toxicity, blood dyscrasias, anaphylaxis

Seizures: Risk of seizures is higher in people with pre-existing CNS disorders or renal impairment (especially when excessive doses are used).

**Dosage**
Adult, IV, 500 mg every 6 hours. Maximum 4 g daily or 50 mg/kg/day, whichever is lower.
Child, IV, 15 mg/kg every 6 hours.
Severe infections
Adult, IV, 1 g every 6–8 hours. Maximum 4 g daily or 50 mg/kg/day, whichever is lower.
Child, IV, 25 mg/kg every 6 hours.
Renal impairment, adult
Mild, IV, 500 mg every 6–8 hours.
Moderate, IV, 500 mg every 8–12 hours.
Severe, IV, 250–500 mg every 12 hours. If creatinine clearance is <5 mL/minute, begin haemodialysis within 48 hours of starting imipenem; give 1 g after dialysis or 500 mg daily.

Administration instructions
Infuse 250–500 mg doses over 20–30 minutes and 1 g doses over 40–60 minutes (more slowly if nausea or vomiting occurs).

Practice points
- contains 1.63 mmol (37.5 mg) sodium per 500 mg
- carbapenems are particularly useful when single agent treatment is required for complex mixed infections; otherwise, combinations of less expensive drugs provide similar antimicrobial cover and clinical efficacy
- P. aeruginosa may develop resistance quickly (resistant to ertapenem)
- Stenotrophomonas maltophilia is intrinsically resistant and may emerge as an opportunistic infection during prolonged treatment
- monitor renal function, hepatic function and complete blood picture during prolonged treatment

Products
IMIPENEM 500 MG+CILASTATIN SODIUM 500 / VIAL (TIENAM®)

MEROPENEM

Mode of action
Inhibit bacterial cell wall synthesis; usually bactericidal; resistant to most beta-lactamases.

Indications
Empirical treatment of nosocomial infections and life-threatening infections (when other antibacterials are inappropriate or contraindicated), or when multi-resistant Gram-negative infections are suspected or proven
Empirical treatment of febrile neutropenic patients
Treatment of severe mixed aerobic and anaerobic infections, particularly when combinations with an aminoglycoside are contraindicated
Exacerbations of lower respiratory tract infections in cystic fibrosis
Meningitis
Meliodosis (with other agents)

Contraindications
Serious allergic reaction to a carbapenem

Specific considerations
Same as Imipenem

Adverse effects
Common: nausea, vomiting, diarrhoea, local injection site reactions, eg phlebitis, thrombocytosis, raised serum transaminases, ALP, bilirubin and lactic hydrogenase
Infrequent: pseudomembranous colitis, itch, rash, headache, eosinophilia, paraesthesia
Rare: anaphylaxis, seizures, thrombocytopenia, neutropenia, agranulocytosis

Dosage
Adult, IV, 0.5–1 g every 8 hours. Maximum 2 g every 8 hours.
Child, IV, 10–20 mg/kg every 8 hours.
Renal impairment
Moderate impairment, IV, 0.5–1 g every 12 hours.
Severe impairment, IV, 0.5 g every 24 hours.
Exacerbation of lower respiratory tract infection in cystic fibrosis
Adult, IV, 1–2 g every 8 hours.
Child, IV, 25–40 mg/kg every 8 hours.
Febrile neutropenia: Adult, IV, 1–2 g every 8 hours.
Meningitis
Adult, IV, 2 g every 8 hours.
Child, IV, 40 mg/kg every 8 hours.

Practice points
- contains 3.92 mmol (90.2 mg) sodium per gram
- carbapenems are particularly useful when single agent treatment is required for complex mixed infections; otherwise, combinations of less expensive drugs provide similar antimicrobial cover and clinical efficacy
- P. aeruginosa may develop resistance quickly (resistant to ertapenem)
- Stenotrophomonas maltophilia is intrinsically resistant and may emerge as an opportunistic infection during prolonged treatment
- monitor renal function, hepatic function and complete blood picture during prolonged treatment

Products
MEROPENEM VIAL (NOT REGISTERED)

05.01.03 Tetracyclines

DOXYCYCLINE

Mode of action
Bacteriostatic; inhibit bacterial protein synthesis by reversibly binding to 30S sub-unit of the ribosome.
Effect of tetracyclines also involves mechanisms other than their antimicrobial activity in acne vulgaris.

Indications
Acne
Infections caused by M. pneumonia
Community-acquired pneumonia
Exacerbation of chronic bronchitis
Acute bacterial sinusitis
Chlamydial (including lymphogranuloma venereum) and other non-gonococcal genital tract infections
PID
Rickettsial infections
Meliodosis (with other agents)
Sexually acquired epididymo-orchitis (with ceftriaxone)
Chronic prostatitis
Prophylaxis of malaria in areas of widespread mefloquine or chloroquine resistance, or in people in whom mefloquine or chloroquine are not tolerated
Treatment of P. falciparum malaria with quinine (allows a shorter course of quinine)

Contraindications
Children <8 years, Allergy to a tetracycline

Specific considerations
Renal impairment: Avoid use.
Systemic lupus erythematosus: exacerbated rarely by tetracyclines.
Treatment with oral retinoids (eg isotretinoin, acitretin): increases risk of benign intracranial hypertension; avoid combination (contraindicated by manufacturer).
Treatment with hepatotoxic drugs: may increase risk of hepatotoxicity.
Renal impairment: It can be used at usual recommended doses in renal impairment.
Hepatic impairment: Hepatotoxicity more likely to occur; avoid high doses.
Children: In children <8 years, tetracyclines cause discoloration of teeth and enamel dysplasia which increases the risk of dental caries. Also deposited in bone, causing deformities and inhibition of bone growth.
Pregnancy: Safe to use during the first 18 weeks of pregnancy (16 weeks post-conception); after this they are contraindicated as they may cause discoloration of baby's teeth; ADEC category D.
Breastfeeding: Theoretical risk of infant teeth discoloration and inhibition of infant bone growth (no cases reported).
Short courses of 7–10 days are considered safe.

Adverse effects
Common: nausea, vomiting, epigastric burning; tooth discoloration, enamel dysplasia, reduced bone growth (in children <8 years); photosensitivity (depends on tetracycline, dose and degree of sun exposure)
Infrequent: rash, stomatitis, bone deformity, fungal overgrowth
Rare: oesophageal ulcers (due to partly swallowed tablets or capsules), pseudomembranous colitis, hepatitis, fatty liver degeneration (with high doses, especially in pregnancy), benign intracranial hypertension, allergic reactions including anaphylaxis (less common than with penicillins), toxic epidermal necrolysis, exacerbation of systemic
lupus erythematosus, serum sickness-like reactions.

**Dosage**

*Adult*, 200 mg on day 1 (as a single dose or 100 mg twice daily), then 100 mg daily. Maximum 200 mg daily.

*Child >8 years*, initially 2 mg/kg twice daily on day 1 (maximum 200 mg daily); then 2 mg/kg once daily (maximum 100 mg daily).

In serious infections the dose can be increased to 4 mg/kg/day (maximum 200 mg) in 1–2 doses.

Round the dose to the nearest 25 mg.

*Acne*: 50 mg daily for at least 6 weeks; titrate dose depending on response.

*Chlamydial infection*: 100 mg twice daily for 1–3 weeks depending on the site and severity of the infection.

*Prophylaxis of malaria*: Start taking 2 days before entering, and continue for 2–4 weeks after leaving, an endemic area. Maximum recommended course 6 months. *Adult*, 100 mg once daily. *Child >8 years*, 2 mg/kg (maximum 100 mg) once daily.

*Treatment of uncomplicated P. falciparum malaria*: *Adult*, 100 mg every 12 hours for 7 days with *quinine*.

*Child >8 years*, 2 mg/kg (maximum 100 mg) every 12 hours for 7 days with *quinine*.

**Patient counselling**

Take with a large glass of water, and remain upright (do not lie down) within 1 hour of taking a tetracycline. This is to stop tablets or capsules sticking on the way to your stomach, and causing painful damage to the lining of your throat.

Avoid sun exposure, wear a hat and use sun screen.

Take doxycycline with food or a glass of milk to reduce stomach upset.

Take a single daily dose in the morning rather than at night.

Do not take antacids, iron, calcium or zinc supplements within 2 hours of doxycycline as they may interfere with its absorption.

*Malaria prophylaxis*: Avoid mosquito bites by using repellents and wearing protective clothing. Begin taking doxycycline 2 days before entering, and continue for 2–4 weeks after leaving, an endemic area. See a doctor if febrile illness develops within 12 months of possible exposure.

**Practice points**

- doxycycline is preferred to tetracycline because it can be given once a day and has fewer adverse effects
- experience with doxycycline for >6 months is limited
- primaquine may be added to doxycycline during the last 2 weeks of prophylaxis to prevent relapses due to *P. vivax or P. ovale* in people returning from prolonged and intense exposure in areas where relapsing malaria is endemic
- doxycycline appears to have fewer adverse effects than mefloquine when used for prophylaxis

**Products**

DOXYCYCLINE CAPS 100 MG (DIOCIMEX®, DOXYDAR®, DOXYMID®, DUMOXIN®, MEDOMYCIN®, REMYCIN®, TABOCIN®, UNIDOX®, VIBRAMYCIN®, ZADORIN®)

**05.01.04 Aminoglycosides**

These include amikacin, gentamicin, neomycin, netilmicin, streptomycin, and tobramycin. All are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin, and tobramycin are also active against Pseudomonas aeruginosa; streptomycin is active against Mycobacterium tuberculosis and is now almost entirely reserved for tuberculosis.

The aminoglycosides are not absorbed from the gut (although there is a risk of absorption in inflammatory bowel disease and liver failure) and must therefore be given by injection for systemic infections. Excretion is principally via the kidney and accumulation occurs in renal impairment.

Most side-effects of this group of antibiotics are dose-related therefore care must be taken with dosage and whenever possible treatment should not exceed 7 days. The important side-effects are ototoxicity, and nephrotoxicity; they occur most commonly in the elderly and in patients with renal failure.

If there is impairment of renal function (or high pre-dose serum concentrations) the interval between doses must be increased; if the renal impairment is severe the dose itself should be reduced as well.

Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis; large doses given during surgery have been responsible for a transient myasthenic syndrome in patients with normal neuromuscular function.

Aminoglycosides should preferably not be given with potentially ototoxic diuretics (e.g. furosemide (frusemide)); if concurrent use is unavoidable administration of the aminoglycoside and of the diuretic should be separated by as long a period as practicable.
Serum concentrations
Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. In patients with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen; patients with renal impairment may require earlier and more frequent measurement of aminoglycoside concentration.
For multiple daily dose regimens, blood samples should be taken approximately 1 hour after intramuscular or intravenous administration (‘peak’ concentration) and also just before the next dose (‘trough’ concentration). For once daily dose regimens, consult local guidelines on serum concentration monitoring.
Serum aminoglycoside concentrations should be measured in all patients and must be determined in infants, in the elderly, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment.

Once daily dosage
Although aminoglycosides are generally given in 2–3 divided doses during the 24 hours, once daily administration is more convenient (while ensuring adequate serum concentration) but local guidelines on dosage and serum concentrations should be consulted.

Endocarditis
Gentamicin is used in combination with other antibiotics for the treatment of bacterial endocarditis. Serum-gentamicin concentration should be determined twice each week (more often in renal impairment). Streptomycin may be used as an alternative in gentamicin-resistant enterococcal endocarditis.
Gentamicin is the aminoglycoside of choice in the UK and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for the ‘blind’ therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole (or both). Gentamicin is used together with another antibiotic for the treatment of endocarditis.
Loading and maintenance doses of gentamicin may be calculated on the basis of the patient’s weight and renal function (e.g. using a nomogram); adjustments are then made according to serum-gentamicin concentrations. High doses are occasionally indicated for serious infections, especially in the neonate or the immunocompromised patient. Whenever possible treatment should not exceed 7 days.
Amikacin is more stable than gentamicin to enzyme inactivation. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.
Neomycin is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Small amounts of neomycin may be absorbed from the gut in patients with hepatic failure and, as these patients may also be uraemic, cumulation may occur with resultant ototoxicity.

AMIKACIN
Mode of action
Inhibit protein synthesis by irreversibly binding to the 30S ribosomal sub-unit. Concentration-dependent bactericidal effect.
Indications
Treatment of infections caused by organisms resistant to other aminoglycosides
Mycobacterial infections (tuberculosis and non-tuberculous)
Parenteral
Empirical treatment of serious Gram-negative infections
Combined treatment with beta-lactams or vancomycin for serious systemic enterococcal infections and endocarditis
Surgical and non-surgical prophylaxis
Contraindications
Serious allergic reaction to an aminoglycoside
Specific considerations
Previous or current treatment with ototoxic or nephrotoxic drugs: more likely to develop aminoglycoside toxicity.
Tinnitus, vertigo, hearing impairment, abnormal audiogram: increased risk of ototoxicity.
Neuromuscular disease (eg myasthenia gravis): increased risk of muscle weakness and respiratory depression.
Hypocalcaemia, hypermagnesaemia, general anaesthesia, large transfusions of citrated blood: increased risk of neuromuscular adverse effects.
Dehydration: increased risk of toxicity.
Renal impairment: Individualise dose based on drug concentration monitoring. Increased risk of nephrotoxicity and ototoxicity as aminoglycosides are predominantly renally cleared. Seek specialist advice; individualise IV/IM dose
based on drug concentration monitoring. 

Surgery: Large doses of aminoglycosides during surgery have caused transient myasthenic syndrome in people with normal neuromuscular function.

Elderly: Use with caution as elderly people are more likely to have pre-existing renal and/or hearing impairment.

Children: Decrease dose in preterm and full term neonates; half-life prolonged.

Pregnancy: Reserve for severe or life-threatening infections for which safer drugs are inappropriate; seek specialist advice for dosing. ADEC category D.

Breastfeeding: Safe to use.

**Adverse effects**

Common: renal impairment, ototoxicity

Rare: anaphylaxis, bronchospasm, *neuromuscular blockade*, oliguria, peripheral neuropathy

Renal impairment: Nephrotoxicity can be anticipated if treatment lasts >7–10 days. Usually presents as gradually worsening non-oliguric renal failure, but may present as acute tubular necrosis. Toxicity is reversible in most cases.

Ototoxicity: Vestibular ototoxicity (nausea, vomiting, vertigo, nystagmus, difficulties with gait) and cochlear ototoxicity (noticeable hearing loss, tinnitus, feeling of fullness in ear) occur in 2–4% of treated people. Pure tone audiometry detects hearing loss in the high tone range (>4000 Hz) in up to 26% of treated people. Ototoxicity is irreversible in 50% of people showing symptoms of hearing loss. Permanent deafness may occur.

Neuromuscular blockade: May result in respiratory depression; can usually be reversed with prompt administration of IV calcium gluconate; the effect of neostigmine is variable.

**Dosage**

Doses listed are a guide for short term treatment (<48 hours) in people with normal renal function; for longer treatment individualise dosage based on drug concentration monitoring. For dosing in people with renal impairment.

Adult: IM/IV, 16–24 mg/kg once daily or in 2–3 divided doses. Use the higher dose for young adults and the lower one for the elderly.

Child: Child >10 years, IM/IV, 18 mg/kg once daily or 15 mg/kg/day in 2–3 divided doses.

Infant, child up to 10 years, IM/IV, 22.5 mg/kg once daily or 7.5 mg/kg 3 times a day. Children >5 years may need a lower dose.

Mycobacterial infections: IM/IV, 15 mg/kg daily 5 times a week with other anti-infective agents.

**Frequency of dosing**

Current evidence in adults and children (including neonates) suggests that once daily dosing is at least as effective as, and no more toxic than, more frequent dosing. Once daily dosing is generally recommended for those with normal renal function.

For patients with burns, bacterial endocarditis, possibly pregnancy, and other conditions where pharmacokinetics may be altered, there is insufficient evidence to justify once daily dosing and dosing every 8–12 hours is still recommended.

Starting doses

Burns, cystic fibrosis, morbidly obese, trauma or intensive care patients have altered pharmacokinetics and require more specialised methods of dosing and monitoring.

Subsequent doses

If treatment is to continue for more than 48 hours, individualise subsequent dosage based on drug concentrations and renal function. May need to extend the dosing interval to 48 hours or longer during renal impairment.

Ideally drug concentration results should be available for interpretation before the next dose is given.
Dosage adjustment is not required if the drug concentration falls within the maximum and minimum lines. If it falls below the minimum line, consider making a proportional increase in dose.

To calculate next dose from the graph, determine target concentration. Calculate next dose in mg/kg as follows:

\[
\text{next dose} = \text{target conc. (mg/L)} \times \text{initial dose (mg/kg)} \div \text{measured conc. (mg/L)}
\]

If the concentration is above the maximum line reassess renal function (creatinine clearance may have been overestimated, or renal function has deteriorated). Then either extend the dosing interval or reduce the dose, using the equation above (if initial dose >4 mg/kg).

**Trough concentrations**

May be monitored to avoid drug accumulation and reduce risk of toxicity, but they do not indicate whether adequate dosage has been given. Trough concentrations may be useful in patients with renal impairment to determine the appropriate interval for repeat doses.

Measure plasma concentration 24 hours after administration of initial dose. If the concentration is <0.5 mg/L, continue the same dose every 24 hours. If it is >0.5 mg/L, extend dosing interval based on creatinine clearance or reduce dose. Repeat monitoring to determine further dosage adjustments at intervals determined by clinical state of the patient. Trough levels are commonly used to monitor multiple daily dosing.

**Target AUC**

The most sophisticated monitoring method. Requires 2 drug concentration samples: the first is taken half an hour after completion of the infusion/injection, the second at a specific time depending on renal function. The 24-hour AUC is calculated using a computer program. Refer to Begg EJ et al. A suggested approach to once-daily aminoglycoside dosing. (*Br J Clin Pharmacol* 1995; 39: 605–609). The AUC can be calculated manually and the target corresponds to 100 mg/L x hour. This method can be used in renal impairment.

Multiple daily dosing: Dosing every 8–12 hours is usually monitored by measuring peak concentration taken 30 minutes after end of injection, or 15-minute infusion, and trough concentration taken just before the next dose. Target peak concentration is >8 mg/L (for amikacin >32 mg/L) and trough concentration is <2 mg/L (for amikacin <8 mg/L). The AUC method can also be used.

**Administration instructions**

Infuse over 15–30 minutes; doses <500 mg may be given as IV injection over 3–5 minutes.

Give parenteral aminoglycosides and penicillins separately as they are physically incompatible.

**Patient counselling**

IV: if you are given this drug for >7–10 days your kidneys may work less well than usual but this should improve when the drug is stopped. Sometimes hearing and balance is affected and there may be some permanent hearing loss. Tell your doctor if your hearing becomes worse or you are unsteady or dizzy (especially when you sit up, stand up or walk).

**Practice points**

- resistant to inactivation by most bacterial enzymes that degrade aminoglycosides
- calculate creatinine clearance in all patients before starting treatment
- to minimise aminoglycoside toxicity:
  - use short treatment periods (7–10 days)
  - dose once daily except in specified indications, see Frequency of dosing
  - monitor drug concentration and serum creatinine if treating for >48 hours, see Concentration monitoring
  - monitor for cochlear toxicity with pure tone audiometry testing (high tone range) every 1–2 weeks during prolonged treatment, eg osteomyelitis and endocarditis
  - monitor clinically for vestibular toxicity
  - ensure adequate hydration
  - be aware of factors increasing risk of toxicity (see Specific considerations)
- if aminoglycoside dosing with concentration monitoring indicates appropriate treatment, then early deterioration of renal function (within 5 days) is usually due to the underlying condition and not to aminoglycoside toxicity; concentration monitoring and dosage adjustment are still required
- if renal function deteriorates, measure aminoglycoside concentration daily; adjust dose if necessary and consider an alternative antibiotic
- treat serious *P. aeruginosa* infections with an aminoglycoside and a broad spectrum anti-pseudomonal penicillin, cefalosporin or carbapenem
Products
AMIKACIN AMPS/VIAL 250 MG/AMP OR VIAL (AS SULFATE) 1 ML AMP/VIAL (SELEMYCIN®)

AMIKACIN AMPS/VIAL 500 MG/AMP OR VIAL (AS SULFATE) 2 ML AMP/VIAL (LIKACIN®, MIACIN®, SELEMYCIN®)

GENTAMICIN
Mode of action
Same as Amikacin
Indications
Empirical treatment of serious Gram-negative infections
Serious systemic enterococcal infections (with beta-lactams or vancomycin)
Surgical and non-surgical prophylaxis
Cystic fibrosis, bronchiectasis (inhalation)
Contraindications
Same as Amikacin
Specific considerations
Same as Amikacin
Adverse effects:
Same as Amikacin
Dosage
Doses listed are a guide for short term treatment (<48 hours) in people with normal renal function; for longer treatment individualise dosage based on drug concentration monitoring. For dosing in people with renal impairment see Dosage in Aminoglycosides.
Adult
IM/IV, 4–7 mg/kg once daily. Use the higher dose for young adults and the lower one for the elderly.
Child
1 month – 10 years, IM/IV 7.5 mg/kg once daily; or 2.5 mg/kg every 8 hours. Children >5 years may need 1.5–2.5 mg/kg/dose every 8 hours.
>10 years, IM/IV 6 mg/kg once daily; or 1–2 mg/kg every 8 hours.
Endocarditis: IV 1–2 mg/kg every 8 hours (with other antimicrobials).
Endocarditis prophylaxis: Use for people at high risk (amoxycillin alone is adequate for those with lower risk).
Adult (genitourinary and GI procedures), 2 mg/kg IV just before procedure or IM 30 minutes before procedure, with amoxycillin or alternative.
Child (genitourinary and GI procedures), 2.5 mg/kg IV just before procedure or IM 30 minutes before procedure, with amoxycillin or alternative.
Surgical prophylaxis: Adult, 2 mg/kg at the time of induction.
Inhalation in cystic fibrosis, bronchiectasis: 80 mg (diluted in sodium chloride 0.9% to 3–4 mL) twice daily
Frequency of dosing and Concentration monitoring:
Same as Amikacin
Administration instructions
Same as Amikacin
Patient counseling
Same as Amikacin
Practice points
• give gentamicin with benzylpenicillin to treat serious enterococcal infections, eg endocarditis; however, if high level gentamicin and/or streptomycin resistance is present (this is increasing in Enterococcus spp.) adding an aminoglycoside is not beneficial
• calculate creatinine clearance in all patients before starting treatment
• to minimise aminoglycoside toxicity:
  o use short treatment periods (7–10 days)
  o dose once daily except in specified indications, see Frequency of dosing
  o monitor drug concentration and serum creatinine if treating for >48 hours, see Concentration monitoring
  o monitor for cochlear toxicity with pure tone audiometry testing (high tone range) every 1–2 weeks during prolonged treatment, eg osteomyelitis and endocarditis
monitor clinically for vestibular toxicity
ensure adequate hydration
be aware of factors increasing risk of toxicity (see Specific considerations)

- if aminoglycoside dosing with concentration monitoring indicates appropriate treatment, then early deterioration of renal function (within 5 days) is usually due to the underlying condition and not to aminoglycoside toxicity; concentration monitoring and dosage adjustment are still required
- if renal function deteriorates, measure aminoglycoside concentration daily; adjust dose if necessary and consider an alternative antibiotic
- treat serious P. aeruginosa infections with an aminoglycoside and a broad spectrum anti-pseudomonal penicillin, cefalosporin or carbapenem

Products
GENTAMYCIN AMPS/VIAL 20 MG/AMP/VIAL (AS SULFATE) 2 ML AMP OR VIAL (GEMYCIN®, NEO ULTRAGENT®, ULTRAGENT®)

GENTAMYCIN AMPS/VIAL 80 MG/AMP/VIAL (AS SULFATE) 2 ML AMP OR VIAL (GEMYCIN®, GENTAMED®, GENTAMICIN BIOCHEMIE®, MEGENTAL®, NEO ULTRAGENT®, ULTRAGENT®)

SPIRAMYCIN
Mode of action
The mechanism of action of spiramycin is not clear; however, it is thought to reversibly bind to the 50 S subunit of bacterial ribosomes, resulting in blockage of the transpeptidation or translocation reactions, inhibiting protein synthesis and subsequent cell growth. It is primarily bacteriostatic, but may be bactericidal against more sensitive strains when used in high concentrations.

Indications
General considerations
Spiramycin is a macrolide antimicrobial agent with activity against gram-positive organisms, including Streptococcus pyogenes (group A beta-hemolytic streptococci), S. viridans, Corynebacterium diphtheriae, and methicillin-sensitive Staphylococcus aureus.

Accepted: Toxoplasmosis (treatment): Spiramycin is used as an alternative agent in the treatment of toxoplasmosis during pregnancy. Pyrimethamine and sulfadiazine combination is considered to be more effective than spiramycin. However, because spiramycin has not been found to be teratogenic and has been found to be safe in the pregnant woman, fetus, and newborn, it is often used to treat toxoplasmosis during pregnancy and congenital toxoplasmosis. Spiramycin reduces the transmission of toxoplasmosis from the pregnant woman to the fetus; however, it will not affect the severity of disease in an already infected fetus.

Spiramycin has not been shown to be clearly effective in the treatment of cryptosporidiosis in immunocompromised patients.

Specific considerations
Patients with hypersensitivity reactions to other macrolides (e.g., erythromycin, azithromycin, clarithromycin, troleandomycin, dirithromycin, josamycin) may also have hypersensitivity to spiramycin.

Pediatrics: Studies performed in infants and children have not demonstrated pediatrics-specific problems that would limit the usefulness of spiramycin in children.

Elderly: No information is available on the relationship of age to the effects of spiramycin in geriatric patients. However, one small pharmacokinetic study showed that elderly patients (73 to 85 years of age) had an elimination half-life that was twice as long as that in younger patients.

Pregnancy: Spiramycin has not been found to be teratogenic, and has been found to be safe in the pregnant woman, fetus, and newborn.

Breast-feeding: Spiramycin is distributed into breast milk.

Adverse Effects
Severe adverse reactions due to spiramycin are rare. Hypersensitivity reactions and gastrointestinal disturbances occur most frequently. Thrombocytopenia, QT prolongation in an infant, cholestatic hepatitis, acute colitis, and ulcerated esophagitis have each only been reported as single case reports in the literature; there were two case reports of intestinal mucosal injury.

Dosage
Usual adult and adolescent dose
Oral, 1 to 2 grams (3,000,000 to 6,000,000 IU) two times a day; or 500 mg to 1 gram (1,500,000 to 3,000,000 IU)
three times a day. For severe infections, the dose may be increased to 2 to 2.5 grams (6,000,000 to 7,500,000 IU) two times a day.

**Toxoplasmosis**

Subclinical congenital infection: Oral, 0.5 to 1 mg per kg of body weight per day of pyrimethamine in combination with 50 to 100 mg per kg of body weight per day of sulfadiazine for four weeks, alternating with 50 to 100 mg (150,000 to 300,000 IU) per kg of body weight of spiramycin for six weeks; these dosing courses are repeated for one year.

Overt congenital infection: Oral, 0.5 to 1 mg per kg of body weight per day of pyrimethamine in combination with 50 to 100 mg per kg of body weight per day of sulfadiazine and folinic acid 5 mg every three days for six months, alternating with 50 to 100 mg (150,000 to 300,000 IU) per kg of body weight of spiramycin in combination with pyrimethamine and sulfadiazine for four weeks; these dosing courses are repeated until 18 months of age.

Toxoplasmosis in pregnant women

First trimester: Oral, 3 grams (9,000,000 IU) per day, divided into three or four doses.

Second and third trimesters: Oral, 25 to 50 mg of pyrimethamine per day in combination with 2 to 3 grams of sulfadiazine per day and folinic acid 5 mg per day for three weeks, alternating with 3 grams (9,000,000 IU) of spiramycin, divided into three or four doses, for three weeks.

Children 20 kg of body weight and over: Oral, 25 mg (75,000 IU) per kg of body weight two times a day, or 16.7 mg (50,000 IU) per kg of body weight three times a day.

**Practice points**

- Cross-resistance between spiramycin and erythromycin has been reported.
- Administration of spiramycin with food reduces bioavailability by approximately 50% and delays the time to peak serum concentration.
- Spiramycin should be taken on an empty stomach.

**Products**

- **SPIRAMYCIN TABS 3,000,000 IU (RAZEX®, ROVAMYCINE®)**
- **SPIRAMYCIN+METRONIDAZOLE TABS 750,000 IU + 125 MG (RODOGYL®, ORAGIN®)**

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### 05.01.05 Macrolides

See also Table 05–01 Drug choice for common infections, Macrolides in Table 05–02 Organism susceptibility to antimicrobials

**AZITHROMYCIN**

**Mode of action**

Bacteriostatic; inhibit bacterial protein synthesis by binding to the 50S ribosomal sub-unit.

**Indications**

- Treatment of choice for chlamydial infections, e.g. urethritis, cervicitis, trachoma
- Streptococcal pharyngitis/tonsillitis
- Community-acquired pneumonia
- Mycobacterium avium intracellulare complex (MAIC) prophylaxis in HIV patients
- Typhoid, paratyphoid (enteric fever)
- Donovonosis (granuloma inguinale)
- Alternatives to penicillins and cefalosporins in people allergic to these drugs
- Pertussis prophylaxis and treatment (erythromycin)
- Chlamyidial infections

**Contraindications**

- Serious allergy to macrolides

**Specific considerations**

- Risk factors for prolonging the QT interval, see Prolonged QT interval: azithromycin has been associated with prolonging the QT interval.
- Hepatic impairment: Use with caution in severe impairment; consider dose reduction.
- Pregnancy: Clarithromycin, contact specialised information service for specific advice; ADEC category B1.
- Breastfeeding: safe to use, but may cause loose bowel actions in infant.
- Clarithromycin, limited data available but considered safe to use.

**Adverse effects**
Common: nausea, vomiting, diarrhoea, abdominal pain and cramps, headache, dyspnoea, cough, candidal infections, inflammation and pain at infusion site (more frequent as the concentration of azithromycin increases)

Infrequent: rash, fixed drug eruptions

Rare: prolonged QT interval, torsades de pointes (both very rare), anaphylaxis, acute respiratory distress, cholestatic hepatitis, Stevens–Johnson syndrome, psychiatric disturbances, hearing loss, pseudomembranous colitis, pancreatitis, convulsions

**Dosage**

Chlamydial infections, part of multi-drug treatment of gonorrhoea, Oral, 1 g as a single dose.

Trachoma: Child >6 months and >6 kg, oral, 20 mg/kg as a single dose once a week for 1–3 weeks. Disease-free period may be increased by giving another dose at 6 months. Adult, oral, 1 g as a single dose once each week for 1–3 weeks.

Streptococcal pharyngitis, tonsillitis: Child >6 months, oral, 10 mg/kg (maximum 500 mg) in a single daily dose for 3 days.

MAC: Treatment, oral, 500 mg daily (alternative to clarithromycin with rifabutin and ethambutol).

Prophylaxis, oral, 1.2 g taken once a week.

Donovanosis (granuloma inguinale): Oral, 500 mg daily for 7 days; or 1 g as a single dose once a week for 4 weeks or until healed.

Community-acquired pneumonia

Adult: IV, 500 mg once daily for at least 2 days, then 500 mg orally daily to complete a 7–10 day course. Oral, 500 mg once on day 1, then 250 mg once daily on days 2–5 or 500 mg once daily for 3 days.

If IV treatment has been given, the dose is 500 mg orally once daily to complete a 7–10 day course.

Child >6 months. Oral, 10 mg/kg (maximum 500 mg) once on day 1, then 2.5 mg/kg (maximum 250 mg) once daily for days 2–5.

Typhoid, paratyphoid

Adult, oral, 500 mg daily for 7 days.

Child, oral, 10 mg/kg daily for 7 days.

Pertussis

Adult, oral, 500 mg on day 1, then 250 mg daily for another 4 days.

Child, oral, 10 mg/kg (maximum 500 mg) on day 1, then 5 mg/kg (maximum 250 mg) for another 4 days.

Maximum: Oral, 1.2 g as a single dose (in MAC).

**Administration instructions**

Give a 500 mg dose IV over at least 1 hour; ideally infuse a concentration of 1 mg/mL over 3 hours and one of 2 mg/mL over 1 hour.

**Practice points**

- consider azithromycin for 5 days for prevention and treatment of pertussis if erythromycin is unsuitable (as effective as erythromycin with fewer adverse effects)
- there is evidence to suggest that prolonged courses of azithromycin in some people with cystic fibrosis may help improve or maintain lung function and decrease the number of antibiotic courses needed
- there is a high degree of cross-resistance between erythromycin and the newer macrolides
- cross-resistance often exists between macrolides and lincosamides (clindamycin and lincomycin)
- the role of newer macrolides is emerging; they are promoted for treatment of community-acquired pneumonia due to their improved activity against H. influenzae and Moraxella catarrhalis; however, increasing pneumococcal resistance may limit future empirical use as single agents

**Products**

AZITHROMYCIN CAPS 250 MG (AS DIHYDRATE) (AZITAM®, AZOMYCIN®, AZOMYNE®, AZOX®, ZIMAX®, ZITHROMAX®, ZOCIN®, ZOMAX®)

AZITHROMYCIN SUSP. 200 MG/ML (AS DIHYDRATE) 15-22.5 ML (AZITAM®, AZOMYNE®, ZIMAX®, ZITHROMAX®, ZOCIN®, ZOMAX®)

AZITHROMYCIN VIAL 500 MG 10 ML (ZITHROMAX®, ZOMAX®)

**CLARITHROMYCIN**

**Mode of action**

Same as Azithromycin.

**Indications**
Prophylaxis and treatment of Mycobacterium avium complex (MAC) and other non-tuberculous mycobacterial infections, with other antimicrobials
Eradication of H. pylori, with other antimicrobials
Lower respiratory tract infections

**Contraindications**
Treatment with cisapride or pimozide (risk of cardiac arrhythmias); ergot alkaloids, serious allergy to macrolides

**Specific considerations**
Same as Azithromycin.

**Adverse effects**
Serious adverse effects are rare.
Common: nausea, vomiting, diarrhoea, abdominal pain and cramps, headache, dyspnoea, cough, candidal infections
Infrequent: rash, fixed drug eruptions
Rare: pulmonary infiltration with eosinophilia, prolonged QT interval, torsades de pointes, anaphylaxis, acute respiratory distress, Stevens–Johnson syndrome, hearing loss, seizures, psychiatric disturbances, pseudomembranous colitis, cholestatic hepatitis, pancreatitis

**Dosage**
Adult, 250–500 mg twice daily.
Child, 7.5 mg/kg twice daily.
Maximum: 1 g twice daily.

MAC
Adult: Treatment, 500 mg twice daily (with rifabutin and ethambutol). Prophylaxis, 500 mg twice daily.
Child: 7.5–15 mg/kg twice daily.
Eradication of H. pylori: 500 mg twice daily for 7 days in combination treatment.

**Moderate-to-severe renal impairment**
Adult: Mild-to-moderate infections, 250 mg daily. Severe infections, 250 mg twice daily.
Child: Reduce dose by half.

**Patient counselling**
This medicine interacts with many drugs; tell your doctor and pharmacist that you are taking this medicine before starting or stopping any medicines, including herbal and over-the-counter products.

**Practice points**
- do not use >500 mg twice daily to treat HIV patients for MAC, as higher doses have been associated with unexplained increased mortality
- there is a high degree of cross-resistance between erythromycin and the newer macrolides
- cross-resistance often exists between macrolides and lincosamides (clindamycin and lincomycin)
- the role of newer macrolides is emerging; they are promoted for treatment of community-acquired pneumonia due to their improved activity against H. influenzae and Moraxella catarrhalis; however, increasing pneumococcal resistance may limit future empirical use as single agents

**Products**
CLARITHROMYCIN SUSP. 125 MG/5ML 100 ML BOTTLE (CLARIDAR®, KLACID®, KLARIMID®)
CLARITHROMYCIN TABS 250 MG (CLARIDAR®, CLARITOP®, CLARIX®, ERACID®, JOCLAR®, KLACID®, KLARIBAC®, KLAXIN®, MACROMAX®)
CLARITHROMYCIN TABS 500 MG (CLARIDAR®, CLARITOP®, CLARIX®, ERACID®, JOCLAR®, KLACID®, KLARIBAC®, KLAXIN®, MACROMAX®, KLARIMID®, KLARIDILID®)

**ERYTHROMYCIN**

**Mode of action**
Same as Azithromycin.

**Indications**
Alternative treatment in people allergic to penicillin
Upper and lower respiratory tract infections
Rheumatic fever prophylaxis (in penicillin allergy)
Legionnaires' disease, Campylobacter enteritis, Coral cuts, Chlamydial infections, including trachoma in children <6 kg and lymphogranuloma venereum (LGV), Pertussis

**Contraindications**
Severe hepatic impairment. Treatment with cisapride or pimozide (risk of cardiac arrhythmias); ergot alkaloids, serious allergy to macrolides

Specific considerations
Risk factors for prolonged QT interval—may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
Treatment with drugs that inhibit CYP3A4, see Some inducers, inhibitors & substrates of CYP450 enzymes: may increase erythromycin concentration and the risk of QT prolongation; avoid combinations if possible.
Myasthenia gravis: erythromycin may aggravate condition.
Renal impairment: Consider reducing dose in severe impairment (deafness may occur with high doses).
Hepatic impairment: Use with caution as may worsen hepatic impairment; contraindicated in severe impairment.
Children: Use with caution in neonates <2 weeks of age as infantile hypertrophic pyloric stenosis can occur; risk increases with length of treatment; consider risk/benefit ratio.
Pregnancy: safe to use; ADEC category A.
Breastfeeding: safe to use, but may cause loose bowel actions in infant.

Adverse effects
Serious adverse effects are rare.
Common: nausea, vomiting, abdominal pain, diarrhoea (dose-related and occur in 5–30% of treated people); headache, dyspnoea, cough, candidal infections, infantile hypertrophic pyloric stenosis (see Infantile hypertrophic pyloric stenosis)
Infrequent: rash, fixed drug eruptions, thrombophlebitis (IV administration), transient deafness (IV administration of high doses), prolonged QT interval, torsades de pointes
Rare: anaphylaxis, acute respiratory distress, Stevens–Johnson syndrome, hearing loss, seizures, psychiatric disturbances, pseudomembranous colitis, cholestatic hepatitis, pancreatitis, myasthenia-like syndrome
Infantile hypertrophic pyloric stenosis: Has occurred in about 5% of a cohort of infants receiving erythromycin for pertussis prophylaxis; risk increased with increasing length of treatment; no increased risk in infants receiving erythromycin after 2 weeks of age.

Dosage
Adult: Oral, 250–500 mg every 6–8 hours. Maximum 4 g daily. Doses <1 g daily can be given in 2 divided doses. IV, 15–20 mg/kg/day in 4 divided doses. Maximum 4 g daily.
Severe pneumonia: IV, 0.5–1 g every 6 hours.
LGV: Oral, 500 mg 4 times a day for 3 weeks.
Child: Oral/IV, 7.5 mg/kg every 6 hours. Maximum 12.5 mg/kg every 6 hours or 15 mg/kg every 8 hours.
Neonatal inclusion conjunctivitis (C. trachomatis) Oral, 10 mg/kg every 6 hours for 3 weeks.
Pertussis prophylaxis and treatment: Adult, oral, 250 mg every 6 hours for 7 days. Child, oral, 10 mg/kg/dose (maximum 250 mg) every 6 hours for 7 days.
Recurrent rheumatic fever prophylaxis: Adult, child, oral, 250 mg every 12 hours.
Campylobacter enteritis: Adult, oral, 500 mg 4 times a day for 7–10 days. Child, oral, 10 mg/kg 4 times a day for 7–10 days.
Severe renal impairment: Reduce dose by quarter to a half.

Administration instructions
Reconstitute injection with water for injection only; dilute further before administration.
Rapid IV administration of erythromycin has resulted in prolonged QT interval and development of serious ventricular arrhythmias.
Parenteral erythromycin formulations are irritant and may cause thrombophlebitis; infuse at a concentration of 1–5 mg/mL over at least 60 minutes, or slowly via a central vein where possible. Avoid extravasation.
Oral therapy should replace IV as soon as possible.
IM injection is painful and not recommended.

Patient counselling
This medicine interacts with many drugs; tell your doctor and pharmacist that you are taking this medicine before starting or stopping any medicines, including herbal and over-the-counter products.
It is best absorbed when taken 1 hour before or 2 hours after meals but if it upsets your stomach take the capsules with food.
Parents of neonates, tell your doctor if your baby develops vomiting or is irritable when feeding while taking erythromycin.

Practice points
stop erythromycin if severe hepatic dysfunction develops
there is a high degree of cross-resistance between erythromycin and the newer macrolides
cross-resistance often exists between macrolides and lincosamides (clindamycin and lincomycin)
the role of newer macrolides is emerging; they are promoted for treatment of community-acquired pneumonia due to their improved activity against H. influenzae and Moraxella catarrhalis; however, increasing pneumococcal resistance may limit future empirical use as single agents

Products
ERYTHROMYCIN SUSP. 200 MG/ML 100 ML BOTTLE
(ERYTHROCIN®, ERYTHRODAR®, ERYTHROMIL®, KOMYCIN®, RYTHROMAC®, RYTHINATE®)

05.01.06 Clindamycin
See also Table 05–01 Drug choice for common infections, Lincosamides in Table 05–02 Organism susceptibility to antimicrobials

CLINDAMYCIN
Mode of action
Bacteriostatic; inhibit protein synthesis by binding to the 50S ribosomal sub-unit.

Indications
Alternative in patients with severe allergy to penicillins and cefalosporins including endocarditis prophylaxis, aspiration pneumonia, dental, skin, soft tissue and bone infections
Toxoplasma encephalitis/abscess (alternative to sulfadiazine)
Bacterial vaginosis
Anaerobic infections
Pneumocystis jiroveci pneumonia (alternative to trimethoprim with sulfamethoxazole)
Acne

Contraindications
Serious allergic reaction to clindamycin or lincomycin

Specific considerations
Hepatic impairment: Clindamycin and metabolites may accumulate, increasing the risk of toxicity; consider dose reduction.
Elderly: Increased risk of pseudomembranous colitis.
Pregnancy: Safe to use; ADEC category A. Use oral clindamycin instead of clindamycin vaginal cream to treat bacterial vaginosis during pregnancy (increased adverse effects with cream e.g. neonatal infections, prematurity,).
Breastfeeding: Safe to use; may cause loose bowel actions in the baby.

Adverse effects
Common: diarrhoea (mild-to-severe), pseudomembranous colitis, nausea, vomiting, abdominal pain or cramps, metallic taste (with high IV doses), rash, itch, contact dermatitis (with topical use)
Rare: anaphylaxis, blood dyscrasias, polyarthritis, jaundice, raised liver enzymes, hepatotoxicity (with high doses)
IV, hypotension, cardiac arrest (rapid injection), thrombophlebitis, toxic epidermal necrolysis, IM, pain, induration, sterile abscess.
Pseudomembranous colitis: Occurs with lincomycin and clindamycin (may affect 2–10% of patients treated with clindamycin); caused by C. difficile toxin. Symptoms range from mild-to-severe diarrhoea to colitis and toxic megacolon, which may be life-threatening. Not dose-related; incidence is similar with oral and parenteral administration (rare with topical use); more frequent in females and elderly people.
Stop clindamycin or lincomycin immediately if patient develops diarrhoea and take faecal samples for detection of toxin. Metronidazole is first line treatment.

Dosage
Adult: Oral, 150–450 mg every 6–8 hours. IV, 600–2700 mg daily given in 2–4 doses, usually 450–900 mg every 8 hours. Maximum IV 4.8 g daily.
Child: Oral, 5–7.5 mg/kg every 6–8 hours. IM/IV, 10 mg/kg every 6–8 hours.
Dental infections: Oral, 300–450 mg every 8 hours for 5–7 days.
Endocarditis prophylaxis (e.g. dental surgery): Adult Oral, 600 mg 1 hour before surgery. IV infusion, 600 mg, complete before procedure starts. Child Oral, 20 mg/kg (maximum 600 mg) 1 hour before surgery.
Bacterial vaginosis (including pregnancy)
Oral, 300 mg twice a day for 7 days. See also Clindamycin.
P. jiroveci pneumonia, treatment
Give with primaquine.
Oral, 300–450 mg every 6 hours.
IV, 600 mg every 6 hours.
Toxoplasma encephalitis/abscess: Treatment, oral/IV, 600 mg every 6 hours, with pyrimethamine, see PYRIMETHAMINE.
Suppressive/maintenance therapy, oral, 600 mg every 8 hours, with pyrimethamine, see PYRIMETHAMINE.

Administration instructions
Dilute in glucose 5% or sodium chloride 0.9% to concentration not >12 mg/mL and infuse slowly IV (not >30 mg/minute) to reduce risk of adverse cardiac effects (hypotension, cardiac arrest). Do not give >1200 mg over 1 hour.

Patient counselling:
Take with a full glass of water. Stop taking this medication and tell your doctor immediately if you develop diarrhoea.
Check with your doctor or pharmacist before taking any antidiarrhoeal medications.

Practice points
- monitor complete blood count, hepatic and renal function during prolonged treatment
- avoid using antidiarrhoal medications, e.g. loperamide, during colitis (toxin may be retained and worsen colitis)
- there is complete cross-resistance between clindamycin and lincomycin
- cross-resistance often exists between lincosamides and macrolides for staphylococci and streptococci

Products:
CLINDAMYCIN AMPS 150 MG/ML (AS HCL) 4 ML AMP (CLINDAMYCINE®, DALACIN C®, DOLINE®)
CLINDAMYCIN CAPS 150 MG (CLINARAM®, CLINDACIN®, CLINDAMYL®, CLINDOX®, CLINIMYCIN®, DALACIN C®, LANACIN®)

05.10.07 Some other antibacterials

05.01.07.01 Chloramphenicol
Chloramphenicol is a potent broad-spectrum antibiotic; however, it is associated with serious haematological side-effects when given systemically and should therefore be reserved for the treatment of life-threatening infections, particularly those caused by Haemophilus influenzae, and also for typhoid fever.
See also Table 05–01 Drug choice for common infections, chloramphenicol in Table 05–02 Organism susceptibility to antimicrobials

CHLORAMPHENICOL

Mode of action
A broad spectrum bacteriostatic agent that inhibits bacterial protein synthesis by binding to the 50S sub-unit of the bacterial ribosome.

Indications:
Severe typhoid/paratyphoid fever when quinolones or broad spectrum Cefalosporins are ineffective or contraindicated
Alternative in people allergic to penicillins or Cefalosporins for meningitis, brain abscess, or acute epiglottitis
Alternative to tetracyclines for rickettsial infections
Alternative for anaerobic and mixed aerobic and anaerobic infections where clindamycin, metronidazole or broad spectrum beta-lactams are not effective or not tolerated

Contraindications
Serious allergic and/or toxic reactions to chloramphenicol. Pre-existing bone marrow depression and/or blood dyscrasias
Specific considerations
Combination with other drugs causing bone marrow depression or aplastic anaemia: increased risk of toxicity.
Active immunisation: development of immunity impaired.
G6PD deficiency: may cause haemolysis (rare in mild forms).
Renal impairment: Bone marrow toxicity may be more likely in renal impairment; check complete blood picture
during treatment and monitor chloramphenicol concentration if necessary.  

Hepatic impairment: Reduce dose according to plasma concentration in severe impairment.  

Children: Neonates and preterm infants are at increased risk of grey syndrome (see Grey syndrome). Avoid use unless there is no alternative treatment, and the infection is life-threatening.  

Pregnancy: If used orally or parenterally near term, there is a theoretical risk of grey syndrome in the neonate; safe for ophthalmic use; ADEC category A.  

Breastfeeding: Limited data for systemic use; may cause loose bowel actions in baby. Safe for ophthalmic use.  

**Adverse effects**  
Common: nausea, vomiting, headache, reversible bone marrow suppression (see Bone marrow suppression)  
Infrequent: glossitis, stomatitis, diarrhoea, pseudomembranous colitis, mild depression, confusion  
Rare: anaphylaxis, grey syndrome (see Grey syndrome), aplastic anaemia (see below), neuropa thy  

**Bone marrow suppression**  
Early, reversible bone marrow suppression occurs frequently and is dose-dependent; more likely to occur with daily doses >4 g; usually presents after 2 weeks of treatment.  

Aplastic anaemia occurs rarely (1 in 18 000 – 50 000 treated people); not dose-dependent and results from irreversible bone marrow suppression, usually presenting after prolonged or repeated treatment. Mortality rate is high; people who survive may develop leukaemia.  

Grey syndrome: Vasomotor collapse in neonates following high IV doses. Symptoms include ashen grey skin, low body temperature, vomiting, irregular and rapid respiration, and lethargy.  

**Dosage**  
Dose of chloramphenicol sodium succinate is expressed in terms of chloramphenicol.  
Adult: IV/oral, 12.5–25 mg/kg every 6 hours. Maximum oral/IV, 4 g daily.  
Child, infant: IV/oral, 12.5–25 mg/kg every 6–8 hours; seek specialist advice.  

**Concentration monitoring**  
Therapeutic range, 5–20 mg/L.  

Serum levels >25 mg/L frequently produce reversible bone marrow depression.  

**Administration instructions**  
Give IV injection over 1–2 minutes. Maximum concentration 100 mg/mL.  

**Practice points**  
- systemic use is limited by its toxicity; do not use for minor infections or prophylaxis; if using a high dose reduce it as soon as possible; avoid repeated courses and prolonged treatment  
- obtain complete blood picture before and during treatment  
- consider stopping treatment if haematologic changes occur  
- broad spectrum bacteriostatic activity against Gram-positive and Gram-negative bacteria (except Pseudomonas spp.) and anaerobes. May be bactericidal to some organisms, including H. influenzae, N. meningitidis and S. pneumoniae. Variable activity against vancomycin-resistant enterococci  

**Products**  
CHLORAMPHENICOL VIAL 1 GM/VIAL (MEDOPHENICOL®)  

05.01.07.03 Vancomycin and teicoplanin  

**TEICOPLANIN**  

**Mode of action**  
Bactericidal; inhibit bacterial cell wall synthesis by preventing formation of cell wall peptidoglycan polymers.  

**Indications**  
Due to the increasing incidence of clinical isolates resistant to vancomycin, eg vancomycin-resistant enterococci (VRE), vancomycin should be reserved for the following uses, as recommended by the Centers for Disease Control Hospital Infection Control Practices Advisory Committee (USA).  

- treatment of serious infections caused by susceptible organisms resistant to penicillins (MRSA and multi-resistant S. epidermidis, MRSE) or in people with serious allergy to penicillins  
- pseudomembranous colitis (relapse or unresponsive to metronidazole treatment)  
- antibacterial prophylaxis for endocarditis following certain procedures (eg some genitourinary and GI procedures) in penicillin-hypersensitive people at high risk of endocarditis  
- surgical prophylaxis for major procedures involving implantation of prostheses (eg cardiac and vascular procedures) in institutions with a high rate of MRSA or MRSE
Contraindications
Serious allergy to vancomycin or teicoplanin

Specific considerations
Allergy to vancomycin: allergic cross reactions between teicoplanin and vancomycin have occurred; use with caution.
Hearing impairment: glycopeptides rarely cause ototoxicity; greater risk with prolonged use and in renal impairment; consider monitoring hearing with prolonged use.
Treatment with nephrotoxic drugs, eg aminoglycosides: increases risk of nephrotoxicity and ototoxicity; monitor renal function and drug concentrations.
Renal impairment: Ototoxicity and nephrotoxicity may be more likely; reduce dose. Reduce frequency of administration after 3 days.
Pregnancy: Contact specialised information service; ADEC category B3.
Breastfeeding: No data available but unlikely to be a problem; may cause loose bowel actions in the baby.

Adverse effects
More common with rapid IV infusions. Seem to be less frequent with teicoplanin; however, there is less clinical experience with teicoplanin.
Common: IM, itch, fever, chills, eosinophilia, pain, erythema
IV, thrombophlebitis
Infrequent: nephrotoxicity (see Nephrotoxicity)
Rare: anaphylaxis, toxic epidermal necrolysis, erythema multiforme, 'red man' or 'red neck' syndrome, superinfection, thrombocytopenia, neutropenia, tinnitus, dizziness, ototoxicity
Nephrotoxicity: Conflicting reports of frequency; rarely seen, but is more common when used with aminoglycosides.
Otoxicity: Vancomycin alone rarely causes ototoxicity; risk is higher with prolonged use and in renal impairment.
Ootoxicity may be enhanced when glycopeptides are combined with other ototoxic drugs, e.g. aminoglycosides.
'Red man' syndrome: Symptoms include erythema, facial and upper torso rash, which may be followed by hypotension, angioedema and itch. The effect is partly due to histamine release after too rapid an IV infusion.
May be treated with antihistamines (e.g. promethazine). Successful administration of glycopeptide is usually possible by increasing the infusion time to >60 minutes. These reactions occur less frequently with teicoplanin.

Dosage
Adult
Severe infections, e.g. septicaemia: IV, initially 6–12 mg/kg (up to 800 mg) every 12 hours for 3 doses, then 6 mg/kg (up to 400 mg) once daily.
Septic arthritis: IV, initially 12 mg/kg (up to 800 mg) every 12 hours for 3 doses, then 12 mg/kg (up to 800 mg) once daily.
Child: Neonate, IV, loading dose 16 mg/kg, then 8 mg/kg once daily.
Child >2 months, IV, 10 mg/kg (maximum 800 mg) every 12 hours for 3 doses, then 6–10 mg/kg IV/IM once daily.
Renal impairment: Mild, usual doses for the first 3 days, then usual dose every 2 days.
Mild-to-moderate and severe, usual doses for the first 3 days, then usual dose every 3 days.

Concentration monitoring
Therapeutic drug monitoring is unnecessary in most cases. Measure trough concentrations when treating severe infections (e.g. endocarditis); maintain trough above 10 mg/L.

Practice points
• teicoplanin is an alternative to vancomycin but is more expensive
• monitor renal function and complete blood picture at least once a week; more frequently during prolonged and/or high dose treatment, in people with impaired renal function and the elderly
• avoid use of other potentially nephrotoxic or ototoxic drugs, eg aminoglycosides
• measurement of vancomycin concentration is unnecessary in most people

Products
TEICOPLANIN VIAL 200 MG/VIAL (TARGOCID®)

VANCOMYCIN
Mode of action
Bactericidal; inhibit bacterial cell wall synthesis by preventing formation of peptidoglycan polymers..
Indications
Due to the increasing incidence of clinical isolates resistant to vancomycin, eg vancomycin-resistant enterococci (VRE), vancomycin should be reserved for the following uses, as recommended by the Centers for Disease Control Hospital Infection Control Practices Advisory Committee (USA).

- treatment of serious infections caused by susceptible organisms resistant to penicillins (MRSA and multi-resistant S. epidermidis, MRSE) or in people with serious allergy to penicillins
- pseudomembranous colitis (relapse or unresponsive to metronidazole treatment)
- antibacterial prophylaxis for endocarditis following certain procedures (eg some genitourinary and GI procedures) in penicillin-hypersensitive people at high risk of endocarditis
- surgical prophylaxis for major procedures involving implantation of prostheses (eg cardiac and vascular procedures) in institutions with a high rate of MRSA or MRSE

Endocarditis prophylaxis in penicillin allergy (for genitourinary and GI procedures add an aminoglycoside)

Severe infections caused by susceptible organisms in cases of penicillin resistance or intolerance, e.g. meningitis, endocarditis (with other agents)

MRSA infections

Pseudomembranous colitis (oral)

Surgical prophylaxis (selected indications only)

**Contraindications**

- Serious allergy to vancomycin or teicoplanin

**Specific considerations**

- Allergy to teicoplanin: allergic cross reactions between teicoplanin and vancomycin have occurred; use with caution.

- Hearing impairment: glycopeptides rarely cause ototoxicity; greater risk with prolonged use and in renal impairment; consider monitoring hearing with prolonged use.

- Treatment with nephrotoxic drugs, eg aminoglycosides: increases risk of nephrotoxicity and ototoxicity; monitor renal function and drug concentrations.

- Renal impairment: Ototoxicity and nephrotoxicity may be more likely; reduce dose. Increase dose interval or reduce dose or both.

- Surgery: Vancomycin may interact with a number of anaesthetic agents; complete vancomycin infusion before induction of anaesthesia.

- Elderly: Increased risk of toxicity.

- Children: Increased risk of nephrotoxicity due to immature renal function, especially in preterm infants.

- Pregnancy: Limited data available; ADEC category B2.

- Breastfeeding

- Safe to use; may cause loose bowel actions in the baby.

**Adverse effects**

- More common with rapid IV infusions.

- Seem to be less frequent with teicoplanin; however, there is less clinical experience with teicoplanin.

- Common: IM, itch, fever, chills, eosinophilia, pain, erythema, IV, thrombophlebitis

- Infrequent: nephrotoxicity

- Rare: anaphylaxis, toxic epidermal necrolysis, erythema multiforme, 'red neck' or 'red man' syndrome, superinfection, thrombocytopenia, neutropenia, leucopenia, tinnitus, dizziness, ototoxicity

- Nephrotoxicity: Conflicting reports of frequency, but appears more common in renal impairment or when used with aminoglycosides; seems less frequent with teicoplanin than vancomycin.

- Otoxicity: Vancomycin alone rarely causes ototoxicity; risk is higher with prolonged use and in renal impairment.

- Otoxicity may be enhanced when glycopeptides are combined with other ototoxic drugs, eg aminoglycosides.

- 'Red man' syndrome: Symptoms include erythema, facial and upper torso rash, which may be followed by hypotension, angioedema and itch. The effect is partly due to histamine release after too rapid an IV infusion. May be treated with antihistamines (eg promethazine). Successful administration of glycopeptide is usually possible by increasing the infusion time to >60 minutes.

- These reactions occur less frequently with teicoplanin.

**Dosage**

- Adult: IV, 500 mg every 6 hours or 1 g every 12 hours.
- Larger doses are required in obese patients (>100 kg); a suggested starting dose is 30 mg/kg/day. More frequent dosing may also be necessary; monitor vancomycin concentration.
- Child: IV, 10–15 mg/kg every 6 hours or 20–30 mg/kg every 12 hours.
- Renal impairment, adult: Use trough concentration monitoring to guide dosage interval; give another dose when concentration is <15 mg/L. Mild, IV, 1 g every 12–24 hours. Moderate, IV, 1 g every 1–5 days. Severe, IV, 1 g every
4–10 days.
Endocarditis prophylaxis: Add gentamicin if the procedure involves the genitourinary or GI tracts.
Adult, IV, 1 g infused over at least 1 hour just before the procedure. Child, IV, 20 mg/kg (up to 1 g) infused over at least 1 hour just before the procedure.
Surgical prophylaxis: IV, 1 g single dose (infusion to be completed before induction of anaesthesia).
Pseudomembranous colitis: Adult, oral, 125 mg every 6 hours for 7–14 days.

Concentration monitoring
Measurement unnecessary in most cases; measure to enable dose individualisation:
- with concomitant aminoglycoside treatment
- in people with altered pharmacokinetics, e.g. burns patients, morbidly obese (may require higher doses due to large volume of distribution and increased drug clearance)
- in patients on haemodialysis receiving infrequent doses of vancomycin (half-life varies according to ultrafiltration rate and dialyser pore size)
- during high dose and/or prolonged treatment
- in patients with unstable or impaired renal function.

Therapeutic range
Trough level 10–20 mg/L taken immediately before next dose (preferably trough should be <10 mg/L if other nephrotoxic agents are being used, e.g. aminoglycosides).
Peak levels for vancomycin have not been proven to correlate with efficacy or toxicity.

Administration instructions
Give via central venous catheter if possible; avoid extravasation; never give IM. Do not mix with other drugs in parenteral solutions.
IV infusion: give over at least 60 minutes (rate not >10 mg/minute for doses >500 mg).

Practice points
- used with an aminoglycoside for serious systemic enterococcal infections (but increased potential for nephrotoxicity with combination)
- reserve oral vancomycin for relapses or serious cases of pseudomembranous colitis unresponsive to metronidazole or bacitracin (if available)

Vancomycin resistance
- resistance is relatively uncommon in organisms normally susceptible to vancomycin
- monitor renal function and complete blood picture at least once a week during therapy.
- there is concern about the increasing incidence of vancomycin resistance in previously susceptible clinical isolates of enterococci and staphylococci; vancomycin-resistant enterococci (VRE) have now been reported worldwide, and are an important public health issue; serious infections caused by these organisms are difficult to treat and carry a poor prognosis. Intermediate and high resistance to vancomycin in S. aureus has also been reported
- restriction of vancomycin use and infection control precautions to prevent transmission are critical to prevent spread of vancomycin resistance
- there is some cross-resistance with teicoplanin
- monitor renal function and complete blood picture at least once a week during parenteral therapy
- avoid use of other potentially nephrotoxic or ototoxic drugs, e.g. aminoglycosides
- measurement of vancomycin concentration is unnecessary in most people

Products
VANCOMYCIN VIAL 500 MG/VIAL (AS HCL) (VANCOCIN® VANCOMYCIN®)

05.01.08 Trimethoprim and Sulphonamides
See also Table 05–01 Drug choice for common infections, trimethoprim with sulfamethoxazole in Table 05–02
Organism susceptibility to antimicrobials, P. jiroveci (P. carinii) pneumonia, Toxoplasmosis

TRIMETHOPRIM WITH SULFAMETHOXAZOLE
Also known as co-trimoxazole.

Mode of action
Sulphonamides and trimethoprim are bacteriostatic; they competitively inhibit bacterial folate production essential for bacterial growth.

Indications
Treatment and primary and secondary prophylaxis of P. jiroveci (P. carinii) pneumonia, see also P. jiroveci (P. carinii) pneumonia
Infections caused by L. monocytogenes (alternative to ampicillin or benzylpenicillin), Nocardia spp., Stenotrophomonas (Xanthomonas) maltophilia
Melioioidosis (with other agents), Shigellosis, Traveller's diarrhoea, Primary prophylaxis of cerebral toxoplasmosis in HIV patients

Contraindications
Serious allergic reaction to sulfonamides and related drugs (sulfonyleureas, celecoxib, thiazide diuretics) or trimethoprim
Late pregnancy, Neonates <4 weeks old, Severe renal impairment, Severe hepatic impairment

Specific considerations
Sulfonamide allergy: cross-sensitivity between sulfonamides and related drugs (sulfonyleureas, thiazide diuretics) is likely.
HIV infection: increases frequency of allergic reactions to drugs; these are often intolerable and may require use of an alternative. Desensitisation may allow trimethoprim with sulfamethoxazole to be reintroduced (see Practice points).
Blood dyscrasias, porphyria and megaloblastic anaemia due to folate deficiency: may be exacerbated.
Systemic lupus erythematosus—may be induced or exacerbated by sulfonamides.
G6PD deficiency: increased risk of haemolysis with sulfonamides.
Slow acetylator phenotype: greater risk of adverse effects with sulfonamides.
Low urine pH: increases risk of crystalluria (sulfamethoxazole poorly soluble at low pH).
Treatment with oral typhoid vaccine: may inactivate vaccine (active against S. typhi), preventing an immune response.
Renal impairment: Increases risk of hyperkalaemia occurring. Reduce dose to avoid sulfamethoxazole accumulation. Hepatic impairment: Consider the risk/benefit ratio as there is an increased risk of hepatitis.
Elderly: Avoid use; increased risk of severe adverse effects.
Children: Sulfamethoxazole is contraindicated in preterm infants and neonates <4 weeks old due to increased risk of kernicterus, as sulfonamides displace bilirubin from plasma albumin.
Pregnancy: Sulfamethoxazole is contraindicated in late pregnancy because of the risk of kernicterus, jaundice and haemolytic anaemia in the neonate; ADEC category C.
Breastfeeding: Safe if neonate is healthy and full-term; avoid if ill, stressed or preterm infant, and in those with hyperbilirubinaemia or G6PD deficiency. Trimethoprim alone is safe to use.

Adverse effects
Incidence of some adverse effects (rash, fever, nausea, neutropenia, thrombocytopenia, raised hepatic transaminases) is substantially higher in patients with AIDS.
Common: fever, nausea (with oral use), vomiting, diarrhoea, anorexia, rash, itch, sore mouth, hyperkalaemia
Infrequent: headache, drowsiness, photosensitivity, blood dyscrasias.
Rare: megaloblastic anaemia, methaemoglobinemia, anaphylactic shock, erythema, Stevens–Johnson syndrome, toxic epidermal necrolysis, pulmonary infiltrates, hypoglycaemia, hepatitis, interstitial nephritis, crystalluria, urinary obstruction with anuria/oliguria, lowered mental acuity, depression, tremor, ataxia (after IV use in HIV patients), pseudomembranous colitis, serum-sickness syndrome, aseptic meningitis

Dosage
Ratio of trimethoprim to sulfamethoxazole is 1:5.
Doses are expressed as: 160/800 mg = trimethoprim 160 mg with sulfamethoxazole 800 mg (equivalent to 1 double strength tablet). 8/40 mg is equivalent to 1 mL of oral liquid.
Mild-to-moderate infections: Adult, oral, 80/400–160/800 mg every 12 hours. Child, oral, 4/20 mg/kg every 12 hours.
Severe infections: Adult, IV, 160/800–320/1600 mg every 12 hours. Child, IV, 5/25 mg/kg every 12 hours.
Maximum: Oral/IV, 20/100 mg/kg daily in divided doses (in P. jiroveci pneumonia).
Renal impairment: Mild, oral/IV, 160/800 mg every 12 hours for 14 days, then 160/800 mg every 24 hours.
Moderate, oral/IV, 160/800 mg every 12 hours for 3 days, then 160/800 mg every 24 hours.
Melioioidosis: Use with another agent, e.g. ceftazidime, meropenem or imipenem. Adult, oral/IV, 320/1600 mg every 12 hours for at least 14 days. Child, oral/IV, 8/40 mg/kg (maximum 320/1600 mg) every 12 hours for at least 14 days.
P. jiroveci pneumonia:
Adult, Treatment, oral/IV, 5/25 mg/kg every 6–8 hours (depending on severity of infection) until improvement occurs, followed by oral (at the same dose) for a total of 21 days. Oral treatment can be used in mild-to-moderate disease when pO2 >70 mm Hg on room air.
Primary or secondary prophylaxis, oral, 80/400–160/800 mg once daily; or 160/800 mg once daily on 3 days a week.
Child: Treatment of severe disease, oral/IV, 5/25 mg/dose (maximum 320/1600 mg) every 6 hours.
Primary or secondary prophylaxis, oral, 5/25 mg/kg daily in one (maximum 160/800 mg/dose) or two (maximum 80/400 mg/dose) doses on 3 days a week.
Shigellosis: Adult, oral, 160/800 mg every 12 hours for 5 days. Child, oral, 4/20 mg/kg (maximum 160/800 mg) every 12 hours for 5 days.
Toxoplasma gondii encephalitis: Primary prophylaxis, oral, 160/800 mg once daily.
Traveller's diarrhoea, prophylaxis, High risk adults (e.g. type 1 diabetes, gastric acid suppression), oral, 160/800 mg daily for up to 3 weeks.
Traveller's diarrhoea, treatment, moderate-to-severe
Adult, oral, 320/1600 mg single dose or 160/800 mg every 12 hours for 3 days.
Child, oral, 8/40 mg/kg (maximum 320/1600 mg) as a single dose or 4/20 mg/kg (maximum 160/800 mg) every 12 hours for 3 days.

Administration instructions
Preferred infusion fluid is glucose 5%. Dilute each ampoule to 100–125 mL; in fluid restricted patients, dilute with 75 mL. Infuse over 60–90 minutes.

Patient counselling
Take this medicine with food to reduce stomach upset. Drink a lot of fluid (at least 2–3 L daily) during prolonged or high dose treatment.
To reduce risk of rash from the sun avoid sun exposure, wear protective clothing and use sunscreen.

Practice points
- use trimethoprim alone for common infections in adults (particularly UTI); trimethoprim with sulfamethoxazole offers no advantage and there is a higher incidence of adverse effects
- during prolonged or high dose treatment monitor complete blood picture and folate status
- to prevent crystalization maintain adequate urine output; recommended adult fluid intake is at least 2–3 L in 24 hours
- monitor renal function each month during prolonged treatment, particularly in people with pre-existing renal impairment
- stop if severe rash develops
- people allergic to, or unable to tolerate, trimethoprim with sulfamethoxazole may benefit from desensitisation (see specialist literature) if use of this agent is considered necessary
- initial drug of choice for most people with P. jiroveci pneumonia, but HIV patients have a higher incidence of fever, dermatological and haematological reactions
- begin corticosteroids at the same time as trimethoprim with sulfamethoxazole during treatment of P. jiroveci pneumonia in patients with HIV and significant hypoxia, to prevent early deterioration and accelerate recovery
- monitor serum potassium if the patient has renal impairment, is taking drugs which can cause hyperkalaemia, or is taking a high dose, e.g. to treat P. jiroveci pneumonia (trimethoprim can cause reversible hyperkalaemia in these circumstances)

Products
TRIMETHOPRIM+SULFAMETHOXAZOLE AMPS 80+400 MG/AMPS (SEPTRIN®)
TRIMETHOPRIM+SULFAMETHOXAZOLE SUSP. 40+200 MG/5 ML 100 ML BOTTLE (BACTRIM®, BALKATRIN®, NORTRIME®, SEPTRIN®, TRIMIDAR M®, TRIMOL®, TRIOMAX ®)
TRIMETHOPRIM+SULFAMETHOXAZOLE TABS 80+400 MG (BACTRIM®, BALKATRIN®, NORTRIME®, SEPTRIN®, SULPRIM®, TRIOMAX ®, TRIMIDAR M®, TRIMOL®, LEGATRIM®)
TRIMETHOPRIM+SULFAMETHOXAZOLE TABS 160+800 MG (BACTRIM®, BALKATRIN®, SEPTRIN®, TRIMIDAR M®)

05.01.09 Anti-tuberculous drugs

Tuberculosis
People with tuberculosis (TB) must be managed by an infectious diseases physician or a respiratory physician, because this is a public health issue and constant surveillance for drug-resistant TB is important.

Rationale for drug use
Drugs may be used to treat latent or established cases. 
Ensure complete cure without relapse. 
Prevent emergence of drug-resistant strains. 
Achieve bacteriological conversion of sputum to negative as quickly as possible, while minimising adverse effects of treatment. 
Minimise transmission to other people. 
Prevent progression of latent infection to clinical disease. 

**Before starting treatment**
Collect specimens (at least 3 sputum samples) for identification of infecting organism and in-vitro susceptibility testing. 
Measure baseline liver and renal function, complete blood picture and visual acuity/colour vision. 
Check for history of alcohol or drug misuse and the likelihood of compliance with treatment. 
Test for HIV (and hepatitis B and hepatitis C if there are risk factors, eg injection drug user). 
Educate the patient and family about the nature of the disease, prognosis, drug administration and side effects, importance of compliance and consequences of non-compliance. 
A Mantoux tuberculin skin test will assist in selecting people for treatment of latent infection. (See specialist literature for dose of tuberculin PPD and interpretation of result.) 
Notify cases of TB to the State or Territory Health Department. 

**When to start treatment**
Active infection: begin treatment after positive identification of Mycobacterium tuberculosis. If clinical and radiological diagnosis seems likely, it may be reasonable to start treatment after specimens have been collected. 
Latent infection: treatment is indicated for the following patients with a positive tuberculin skin test and no evidence of active disease:
- HIV infected patients 
- people whose skin test has recently become positive 
- people who are recent contacts of an infectious case of TB 
- children 
- immunosuppressed people 
- radiological findings suggesting previous TB. 

**Drug choice**
First line: These drugs have greater activity with acceptable toxicity. This group includes isoniazid, rifampicin, ethambutol and pyrazinamide. In developing countries streptomycin is also a first line drug. 
Second line: These drugs are generally less effective and are used when organisms have developed resistance or adverse effects have occurred with first line drugs. They are also used for non-tuberculous mycobacteria. Second line drugs include amikacin, azithromycin, cycloserine, capreomycin, rifabutin, clarithromycin, ethionamide, streptomycin, gatifloxacin, moxifloxacin and prothionamide. They are generally used in regimens with 5 or 6 drugs. 
Other drug treatment 
Corticosteroids—people with tuberculous meningitis may benefit from corticosteroids in addition to antitubercular treatment. Corticosteroids are also indicated for tuberculous pericarditis and possibly for peritonitis. Do not use in people with latent disease as corticosteroids may cause reactivation. 

**Treatment regimens**

**Active infection**
Multi-drug treatment is always used. A 6-month regimen is usually recommended for sensitive strains. Use an initial intense 2-month course of 4 drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) to achieve rapid reduction in viable organisms, followed by a 4-month course of 2 drugs (isoniazid, rifampicin) to eliminate slowly dividing organisms and prevent relapse. Undertreatment can occur if the correct number of doses have not been taken within a sufficient period of time. Drugs can be taken daily, twice a week or 3 times a week; dosage regimens recommended by various authorities differ slightly. 
If the initial intensive 2-month treatment is not tolerated, drug resistance is shown or there is extensive disease, treatment should be extended or second line drugs added. 
Directly observed therapy (DOT) with a regimen given 2–3 times a week by a health worker is recommended by the Centers for Disease Control and Prevention and the WHO; this improves compliance and allows close monitoring of progress. People who may benefit from DOT include those who have difficulty with compliance, HIV, drug resistance, failed treatment, or relapsed. 
Treatment may be prolonged in more complicated cases, eg extrapulmonary TB, bone and CNS disease, or if response is slow.
Use rifabutin rather than rifampicin in people who are also infected with HIV and are being treated with combination antiretroviral therapy as treatment is complicated by drug interactions with rifampicin. Twice weekly regimens are not recommended if the CD4 cell count is <100 cells/microlitre. Prolonged treatment may be needed; patients should only be managed by specialists with HIV and TB expertise.

Latent infection
In general, treatment is recommended for people <35 years with any of the risk factors listed in When to start treatment. Above this age the risk/benefit ratio for drug treatment is greater and treatment is indicated only for those at higher risk of developing active TB, such as HIV patients or recent tuberculin converters who are contacts of a smear positive TB patient. Radiological checks alone may be recommended for other people >35 years.

Isoniazid should be given for 9 months with daily pyridoxine to prevent peripheral neuropathy. Rifampicin with pyrazinamide is not recommended due to the increased risk of hepatotoxicity.

Factors influencing drug selection
Drug resistance: Approximately 11% of Australian TB isolates are resistant to 1 or more of the 4 standard antitubercular drugs; longer treatment courses are generally required for patients with resistant infections. The 4-drug phase of treatment should be continued for at least 2 months, after which pyrazinamide and ethambutol should be stopped only if the organism is found to be fully drug-sensitive and sputum smears (if obtainable) are negative for acid-fast bacilli. However, ethambutol can be stopped earlier if sensitivity results indicate that the organism is susceptible to rifampicin and isoniazid.

Patients who remain culture positive after the first 2 months of treatment need evaluation, with a strong suspicion of drug resistance or non-compliance.

Adverse effects
Emphasise that drugs should be taken despite minor adverse effects.
GI: taking drugs (including rifampicin) with food or changing the administration time may ease GI adverse effects without affecting their efficacy.
Hepatitis: when serum AST >3 times upper limit of normal with symptoms (or >5 times upper limit of normal without) stop isoniazid, rifampicin and pyrazinamide, test for viral hepatitis and exclude other causes. Substitute alternative agents until the cause is known. After recovery the original drugs can be gradually restarted with careful monitoring.
Allergic reactions: stop all antitubercular drugs (check platelets if there is a petechial rash; if the count is low, stop rifampicin only). Treat the allergy symptomatically (include corticosteroids if the reaction is severe). When allergic symptoms have subsided, cautiously re-introduce each drug sequentially to identify the responsible drug(s), using low doses initially (eg isoniazid 50 mg daily, rifampicin 150 mg daily, pyrazinamide 250 mg daily, ethambutol 100 mg daily). More formal desensitisation may be attempted for particularly severe reactions.

Treatment endpoints
Clinical improvement is usually obvious within 2 weeks of appropriate treatment.
Over 90% of patients receiving appropriate treatment will have negative sputum cultures within 3 months. For people who continue to have a productive cough, examine sputum each month until chemotherapy is completed, and then less frequently for a total of 2 years (sufficient providing the chest x-ray is stable and cultures are negative). If sputum cannot be produced, respiratory samples are needed only for those people not responding clinically or radiologically to treatment.

Treatment Phases
Tuberculosis is treated in two phases: an initial phase using at least three drugs and a continuation phase using two drugs in fully sensitive cases. Treatment requires specialised knowledge, particularly where the disease involves resistant organisms or non-respiratory organs.
The regimens given below are recommended for the treatment of tuberculosis in the UK; variations occur in other countries. Either the unsupervised regimen or the supervised regimen described below should be used; the two regimens should not be used concurrently.

Initial phase
The concurrent use of 4 drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. The drugs are best given as combination preparations unless one of the components cannot be given because of resistance or intolerance. The treatment of choice for the initial phase is the daily use of isoniazid, rifampicin, pyrazinamide and ethambutol. The initial phase drugs should be continued for 2 months. Where a positive culture for M. tuberculosis has been obtained, but susceptibility results are not available after 2 months, treatment with pyrazinamide and ethambutol should be continued until full susceptibility is confirmed, even if this is for longer than 2 months.
Continuation phase
After the initial phase, treatment is continued for a further 4 months with isoniazid and rifampicin (preferably given as a combination preparation). Longer treatment is necessary for meningitis and for resistant organisms which may also require modification of the regimen.

Unsupervised treatment
The following regimen should be used for patients who are likely to take antituberculous drugs reliably without supervision. Patients who are unlikely to comply with daily administration of antituberculous drugs should be treated with the regimen described under Supervised Treatment.
Recommended dosage for standard unsupervised 6-month treatment
Rifampicin, isoniazid, and pyrazinamide for 2-month initial phase only, adult under 40 kg 3 tablets daily, 40–49 kg 4 tablets daily, 50–64 kg 5 tablets daily, over 65 kg 6 tablets daily
Ethambutol for 2-month initial phase only, adult and child 15 mg/kg daily
Rifampicin and isoniazid for 4-month continuation phase following initial treatment rifampicin, isoniazid and pyrazinamide, adult under 50 kg 3 tablets daily of Rifinah®-150, 50 kg and over, 2 tablets daily of Rifinah®-300 or (if combination preparations not appropriate):
Isoniazid (for 2-month initial and 4-month continuation phases): adult 300 mg daily; child 5–10 mg/kg (max. 300 mg) daily
Rifampicin (for 2-month initial and 4-month continuation phases): adult under 50 kg 450 mg daily, 50 kg and over 600 mg daily; child 10 mg/kg (max. 600 mg) daily
Pyrazinamide (for 2-month initial phase only): adult under 50 kg 1.5 g daily, 50 kg and over 2 g daily; child 35 mg/kg daily
Ethambutol (for 2-month initial phase only): adult and child 15 mg/kg daily

Pregnancy and breast-feeding
The standard regimen (above) may be used during pregnancy and breast-feeding. Streptomycin should not be given in pregnancy.

Children
Children are given isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months followed by isoniazid and rifampicin during the next 4 months. However, care is needed in young children receiving ethambutol because of the difficulty in testing eyesight and in obtaining reports of visual symptoms (see below).

Supervised treatment
Drug administration needs to be fully supervised (directly observed therapy, DOT) in patients who cannot comply reliably with the treatment regimen. These patients are given isoniazid, rifampicin, pyrazinamide and ethambutol (or streptomycin) 3 times a week under supervision for the first 2 months followed by isoniazid and rifampicin 3 times a week for a further 4 months.
Recommended dosage for intermittent supervised 6-month treatment
Isoniazid (for 2-month initial and 4-month continuation phases): adult and child 15 mg/kg (max. 900 mg) 3 times a week
Rifampicin (for 2-month initial and 4-month continuation phases): adult 600–900 mg 3 times a week; child 15 mg/kg (max. 900 mg) 3 times a week
Pyrazinamide (for 2-month initial phase only): adult under 50 kg 2 g 3 times a week, 50 kg and over 2.5 g 3 times a week; child 50 mg/kg 3 times a week
Ethambutol (for 2-month initial phase only): adult and child 30 mg/kg 3 times a week

Immunocompromised patients
Multi-resistant Mycobacterium tuberculosis may be present in immunocompromised patients. The organism should always be cultured to confirm its type and drug sensitivity. Confirmed M. tuberculosis infection sensitive to first-line drugs should be treated with a standard 6-month regimen; after completing treatment, patients should be closely monitored. The regimen may need to be modified if infection is caused by resistant organisms, and specialist advice is needed.
Specialist advice should be sought about tuberculosis treatment or chemoprophylaxis in a HIV-positive individual; care is required in choosing the regimen and in avoiding potentially hazardous interactions. Starting antiretroviral treatment in the first 2 months of antituberculosis treatment increases the risk of immune reconstitution syndrome. Infection may also be caused by other mycobacteria e.g. M. avium complex in which case specialist advice on management is needed.

Prevention of tuberculosis
Some individuals may develop tuberculosis owing to reactivation of previously latent disease. Chemoprophylaxis may be required in those who have evidence of latent tuberculosis and are receiving treatment with
immunosuppressants (including cytotoxics and possibly long-term treatment with systemic corticosteroids). In these cases, isoniazid chemoprophylaxis may be given for 6 months; longer chemoprophylaxis is not recommended.

**Monitoring**

Since isoniazid, rifampicin and pyrazinamide are associated with liver toxicity, hepatic function should be checked before treatment with these drugs. Those with pre-existing liver disease or alcohol dependence should have frequent checks particularly in the first 2 months. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. In view of the need to comply fully with antituberculous treatment on the one hand and to guard against serious liver damage on the other, patients and their carers should be informed carefully how to recognise signs of liver disorders and advised to discontinue treatment and seek immediate medical attention should symptoms of liver disease occur.

Renal function should be checked before treatment with antituberculous drugs and appropriate dosage adjustments made. Streptomycin or ethambutol should preferably be avoided in patients with renal impairment, but if used, the dose should be reduced and the plasma-drug concentration monitored.

Visual acuity should be tested before ethambutol is used (see below). Major causes of treatment failure are incorrect prescribing by the physician and inadequate compliance by the patient. Monthly tablet counts and urine examination (rifampicin imparts an orange-red coloration) may be useful indicators of compliance with treatment. Avoid both excessive and inadequate dosage. Treatment should be supervised by a specialist physician.

Isoniazid is cheap and highly effective. Like rifampicin it should always be included in any antituberculous regimen unless there is a specific contra-indication. Its only common side-effect is peripheral neuropathy which is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, malnutrition and HIV infection. In these circumstances pyridoxine 10 mg daily (or 20 mg daily if suitable product not available) should be given prophylactically from the start of treatment. Other side-effects such as hepatitis (important: see Monitoring above) and psychosis are rare.

Rifampicin, a rifamycin, is a key component of any antituberculous regimen. Like isoniazid it should always be included unless there is a specific contra-indication.

During the first two months (‘initial phase’) of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require interruption of treatment. Occasionally more serious liver toxicity requires a change of treatment particularly in those with pre-existing liver disease (important: see Monitoring above).

On intermittent treatment six toxicity syndromes have been recognised—influenza-like, abdominal, and respiratory symptoms, shock, renal failure, and thrombocytopenic purpura—and can occur in 20 to 30% of patients.

Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens, corticosteroids, phenytoin, sulphonylureas, and anticoagulants; Important: the effectiveness of hormonal contraceptives is reduced and alternative family planning advice should be offered.

Rifabutin, a newly introduced rifamycin, is indicated for prophylaxis against M. avium complex infections in patients with a low CD4 count; it is also licensed for the treatment of non-tuberculous mycobacterial disease and pulmonary tuberculosis. Important: as with rifampicin it induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced requiring alternative family planning methods.

Pyrazinamide [unlicensed] is a bactericidal drug only active against intracellular dividing forms of Mycobacterium tuberculosis; it exerts its main effect only in the first two or three months. It is particularly useful in tuberculous meningitis because of good meningeal penetration. It is not active against M. bovis. Serious liver toxicity may occasionally occur (important: see Monitoring above).

Ethambutol is included in a treatment regimen if isoniazid resistance is suspected; it can be omitted if the risk of resistance is low.

Side-effects of ethambutol are largely confined to visual disturbances in the form of loss of acuity, colour blindness, and restriction of visual fields. These toxic effects are more common where excessive dosage is used or if the patient’s renal function is impaired. The earliest features of ocular toxicity are subjective and patients should be advised to discontinue therapy immediately if they develop deterioration in vision and promptly seek further advice. Early discontinuation of the drug is almost always followed by recovery of eyesight. Patients who cannot understand warnings about visual side-effects should, if possible, be given an alternative drug. In particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately.

Visual acuity should be tested by Snellen chart before treatment with ethambutol.

Streptomycin [unlicensed] is now rarely used in the UK except for resistant organisms. It is given intramuscularly in a dose of 15 mg/kg (max. 1 g) daily; the dose is reduced in those under 50 kg, those over 40 years or those with renal
impairment. Plasma-drug concentration should be measured in patients with impaired renal function in whom streptomycin must be used with great care. Side-effects increase after a cumulative dose of 100 g, which should only be exceeded in exceptional circumstances. Drug-resistant tuberculosis should be treated by a specialist physician with experience in such cases, and where appropriate facilities for infection-control exist. Second-line drugs available for infections caused by resistant organisms, or when first-line drugs cause unacceptable side-effects, include amikacin, capreomycin, cycloserine, newer macrolides (e.g. azithromycin and clarithromycin).

See Table 05–05 Antitubercular drugs comparative information

**ETHAMBUTOL**

**Mode of action**
Its mechanism of action is unknown, but it may inhibit incorporation of mycolic acid into the mycobacterial cell wall.

**Indications**
Primary treatment and re-treatment of TB  
Mycobacterium avium complex (MAC)

**Contraindications**
Optic neuritis

**Specific considerations**
Visual defects: see specialist literature for recommendations on testing procedures.  
Renal impairment: Reduce dosage.  
Elderly: Do not use if vision is impaired.  
Children: Do not use in children <6 years as eye tests used to monitor for adverse effects are difficult to carry out.  
Pregnancy: Safe to use; ADEC category A.  
Breastfeeding: Safe to use.

**Adverse effects**
Most are dose-related and are reversible on stopping ethambutol.  
Common: optic neuritis (with daily doses >15 mg/kg), usually reversible, characterised by decreased visual acuity, scotoma or colour blindness  
Infrequent: GI disturbances, acute gouty arthritis, headache, confusion, disorientation, hallucinations, malaise  
Rare: jaundice, peripheral neuritis, hyperuricaemia, neutropenia, eosinophilia, thrombocytopenia, renal failure, allergic reaction (rash, fever, joint pain)

**Dosage**
**TB**
Doses may need adjustment if significant weight gain occurs during treatment. Treat for 2 months; may be stopped after 2 months if organism is sensitive to the other 3 drugs used in the standard 6-month regimen.  
Adult, child >6 years  
Daily regimen, 15–20 mg/kg daily (maximum 1.6 g) for first 2 months, then 15 mg/kg daily if there is a need to continue beyond 2 months.  
Three times a week regimen, 25–30 mg/kg (maximum 2.4 g) 3 times each week.  
Twice a week regimen, 45 mg/kg (maximum 4 g) twice each week.  
MAC: 25 mg/kg daily for 2 months, then 15 mg/kg daily in multi-drug regimen.  
Renal impairment: Mild-to-moderate, usual daily dose every 24–36 hours. Severe, usual daily dose every 48 hours.  

**Patient counselling**
Stop drug immediately and tell your doctor if you have any change in your eyesight.

**Practice points**
- measure renal function at start of treatment  
- monitor visual acuity/colour vision at start of treatment and each month if the dose is >15 mg/kg, if treating for >2 months or there is renal impairment

**Products**
ETHAMBUTOL TABS 400 MG (AS HCL) (NOT REGISTERED)

**ISONIAZIDE**
Also known as INH.

**Mode of action**
The mechanism of action is unknown, but may involve inhibition of synthesis of mycolic acids, constituents of the mycobacterial cell wall.
Indications
Treatment and re-treatment of TB
Treatment of latent TB

Contraindications
Severe adverse reaction to isoniazid

Specific considerations
Severe malnutrition, diabetes, renal impairment, HIV infection: greater risk of peripheral neuropathy (use pyridoxine 25 mg daily as prophylaxis).
Alcoholism: greater risk of peripheral neuropathy (use pyridoxine 25 mg daily as prophylaxis) and hepatotoxicity.
Epilepsy: isoniazid may cause seizures; ensure adequate control.
Treatment with cycloserine: increases the risk of CNS toxicity, eg drowsiness; monitor closely.
Treatment with hepatotoxic drugs, eg rifampicin: increases risk of hepatotoxicity.
Age >35 years: increases risk of hepatotoxicity.
Hepatic impairment: Risk of hepatotoxicity may be increased; use with caution. Start with reduced dosage and monitor liver function tests closely. If liver is not tender and bilirubin is normal, full doses of isoniazid may be used with regular monitoring of liver function. Do not start treatment if ALT level is >2–3 times upper limit of normal.
Elderly: Risk of hepatotoxicity increases with age, especially in females >60 years.
Pregnancy: Safe to use; give with pyridoxine 25 mg daily; the neonate of a mother with TB should also receive isoniazid for 3–6 months; ADEC category A.
Breastfeeding: Safe to use; give with pyridoxine 25 mg daily.
Women: Risk of hepatotoxicity may be greater, especially postpartum.

Adverse effects
Common: rash, fever, peripheral neuritis (if pyridoxine is not given concurrently, or if given with NRTIs, eg didanosine), increased transaminases, hepatitis (see Liver function), acne, tiredness, reduced alertness, raised antinuclear antibodies (without clinical symptoms of systemic lupus erythematosus)
Infrequent: seizures, toxic encephalopathy, optic neuritis and atrophy, memory impairment, toxic psychosis
Rare: pellagra, gynaecomastia, amenorrhoea, urinary retention, hyperglycaemia, agranulocytosis, thrombocytopenia, haemolytic anaemia, lupus-like syndrome, arthritic symptoms, hypersensitivity (fever, rash, vasculitis)
Liver function: Increases in serum transaminases occur in 10–20% of people in the first few months of treatment (but can occur at any time); this usually resolves despite continuation of drug. However, it can progress to more serious hepatic dysfunction sometimes without obvious symptoms. Risk of hepatitis depends on age (35–50 years: 1.2%; >50 years: 2.3%); is higher in patients who regularly use alcohol and when isoniazid is given with rifampicin.

Dosage
Pyridoxine 25 mg with each dose of isoniazid is recommended to reduce the risk of peripheral neuropathy, especially for people at risk.
Treatment of TB: Use as part of a multi-drug regimen. Doses may have to be adjusted if significant weight gain occurs during treatment.
Adult
Daily regimen, 5 mg/kg (maximum 300 mg) daily.
Three times a week regimen, 15 mg/kg (maximum 600 mg) 3 times each week.
Twice a week regimen, 15 mg/kg (maximum 900 mg) twice each week.
Child
Daily regimen, 10 mg/kg (maximum 300 mg) daily.
Three times a week regimen, 20–30 mg/kg (maximum 600 mg) 3 times each week.
Twice a week regimen, 20–30 mg/kg (maximum 900 mg) twice each week.

Treatment of latent infection
Adult, 300 mg daily for 6 months (up to 9–12 months or longer if immunosuppressed, including HIV patients).
Child, 10 mg/kg (maximum 300 mg) daily for 6 months (up to 9–12 months or longer if immunosuppressed, including HIV patients).
Hepatic impairment: Begin with a reduced dose; increase to full therapeutic doses if tolerated.

Patient counselling
Isoniazid can affect your liver and vision, as well as occasionally causing allergy. Stop treatment and tell your doctor if you get persistent nausea, vomiting, unusual tiredness or jaundice, changes in your vision, fever or rash.

Practice points
• monitor transaminase concentrations at baseline and then each month as serious hepatotoxicity can occur without symptoms
- stop isoniazid if transaminase concentrations increase to >5 times the normal upper limit (or >3 times the normal upper limit with symptoms), or the bilirubin concentration rises
- stop isoniazid if symptoms of hypersensitivity occur

ISONIAZIDE TABS 100 MG (NOT REGISTERED)

KANAMYCIN

Mode of action
Inhibit protein synthesis by irreversibly binding to the 30S ribosomal sub-unit and causing cell membrane damage.

Concentration-dependent bactericidal effect.

Indications
Kanamycin is an aminoglycoside antibacterial with actions similar to those of gentamicin. It has been used in the treatment of susceptible Gram-negative and staphylococcal infections, including gonorrhoea and neonatal gonococcal eye infections, although its use has declined in many centres because of the development of resistance. Kanamycin has also been used as a second-line drug in tuberculosis, but other, safer drugs are usually preferred.

Adverse Effects, Treatment, and Precautions
As for Gentamicin Sulfate,
Peak plasma concentrations of kanamycin greater than 30 micrograms/mL, and trough concentrations greater than 10 micrograms/mL, should be avoided. Auditory (cochlear) toxicity is more frequent than vestibular toxicity.
Local pain and inflammation, as well as bruising and haematoma, have been reported at the site of intramuscular injections.
Gastrointestinal disturbances and a malabsorption syndrome, similar to that seen with oral neomycin, have occurred after oral kanamycin. Oral kanamycin should be avoided in patients with gastrointestinal ulceration.
Breast feeding: Although kanamycin is distributed into breast milk the American Academy of Pediatrics states that no adverse effects have been observed in breast-fed infants whose mothers were receiving kanamycin, and therefore considers that its use is usually compatible with breast feeding.

Dosage
A single intramuscular dose of 2 g of kanamycin has been used in the treatment of penicillin-resistant gonorrhoea. In the treatment and prophylaxis of neonatal gonococcal infections in infants born to mothers with gonorrhoea, 25 mg/kg, up to a maximum of 75 mg, may be given as a single intramuscular dose.
Peak plasma concentrations greater than 30 micrograms/mL and trough concentrations greater than 10 micrograms/mL should be avoided. It is recommended that dosage should be adjusted in all patients according to plasma-kanamycin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements.
Kanamycin has been used by mouth similarly to neomycin, for the suppression of intestinal flora. For pre-operative use, 1 g may be given every hour for 4 hours, then 1 g every 6 hours for 36 to 72 hours. In the management of hepatic encephalopathy, 8 to 12 g daily in divided doses may be given.
Kanamycin has also been administered in doses of 250 mg as a nebulised inhalation, 2 to 4 times daily. Solutions of kanamycin 0.25% have been used for the irrigation of body cavities.
Kanamycin tannate has also been used.

Products
KANAMYCIN VIAL 1 GM/VIAL (AS SULFATE) 2 ML VIAL (NOT REGISTERED)

PARAMINOSALICYLIC ACID

Mode of action
Exact mechanism unknown.

Indications
Treatment of mild to moderate ulcerative colitis and maintenance of remission.

Contraindications
Aminosalicylates should be avoided in salicylate hypersensitivity.

Specific considerations
Coexisting conditions
Aminosalicylates should be used with caution in renal impairment.
Pregnancy: avoid use it, ADEC category C.
Breastfeeding: avoid use it.

Adverse effect
Common: Diarrhea, nausea, vomiting, abdominal pain, exacerbation of symptoms of colitis, headache, hypersensitivity reactions (including rash and urticaria).
Rare: acute pancreatitis, hepatitis, myocarditis, pericarditis, lung disorders, peripheral neuropathy, blood disorders (including agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinemia, neutropenia, and thrombocytopenia), renal dysfunction, myalgia, arthralgia, skin reactions (including lupus erythematosus-like syndrome, Steven-Johnson syndrome), alopecia.

Products
PARAAMINOSALYCILIC ACID AMPS (NOT REGISTERED)

PYRAZINAMIDE
Mode of action
It has a bactericidal effect on mycobacteria via an unknown mechanism, but one proposal is that it is converted by bacterial pyrazinamidase to pyrazinoic acid which lowers intracellular pH within macrophages to levels toxic for Mycobacterium tuberculosis

Indications
Primary treatment and re-treatment of TB
Contraindications
Significant liver disease, Porphyria

Specific considerations
Gout: pyrazinamide inhibits the renal excretion of urate and raises uric acid levels.
Diabetes: management may become more difficult.
Renal impairment: Avoid use in moderate-to-severe impairment as accumulation of uric acid crystals may worsen severe impairment.
Pregnancy: Safe to use; ADEC category B2.
Breastfeeding: contact a drug information centre.

Adverse effects
Common: hyperuricaemia, polyarthralgia, nausea
Infrequent: urticaria, itch, dysuria, hepatotoxicity, rash, allergic reactions
Rare: pellagra, sideroblastic anaemia, thrombocytopenia, acute porphyrin crisis, photosensitivity, acute gout
Hepatotoxicity: Rare with doses <25 mg/kg/day; varies from asymptomatic elevation of liver enzymes, a syndrome of fever, anorexia, malaise, liver tenderness, hepatomegaly and splenomegaly, to serious reactions such as clinical jaundice and massive hepatic necrosis. The combination with rifampicin increases the risk of serious hepatic damage, especially in HIV-negative people.

Dosage
Use for 2 months as part of multi-drug regimen. Doses may need adjustment if significant weight gain occurs during treatment.
Adult
Daily regimen, 20–25 mg/kg (maximum 2 g) daily.
Three times a week regimen, 50 mg/kg (maximum 3 g) 3 times each week.
Twice a week regimen, 70 mg/kg (maximum 4 g) twice each week.
Child
Daily regimen, 15–30 mg/kg (maximum 2 g) daily.
Three times a week regimen, 50 mg/kg (maximum 2 g) 3 times each week.
Twice a week regimen, 50 mg/kg (maximum 2 g) twice each week.

Patient Counselling
Stop treatment and tell your doctor if you get continuous nausea, vomiting, unusual tiredness, yellowing of the skin or whites of eyes, dark urine or pale faeces.

Practice points
- pyrazinamide is not active against non-tubercular mycobacteria
- stop pyrazinamide after treating for 2 months only if the organism is sensitive to rifampicin and isoniazid
- before treatment obtain full blood count, serum uric acid, creatinine, urea and liver transaminase concentrations
- repeat serum uric acid if clinical gout occurs
- repeat serum transaminase concentrations if baseline tests are abnormal, if clinical symptoms of hepatitis develop, or if there is heavy alcohol intake
- interrupt treatment if transaminase concentrations are elevated to >5 times the normal upper limit, or bilirubin concentration rises; re-introduce cautiously once liver function returns to normal
• rifampicin with pyrazinamide is not recommended for treatment of latent tuberculosis due to the increased risk of hepatic injury (combination is acceptable for treating active tuberculosis)

**Products**

**PYRAZINAMIDE TABS 500 MG (PYRAZINE®)**

**RIFAMPICIN**

**Mode of action**

Rifampicin is a derivative of rifamycin B and rifabutin is a derivative of rifamycin S. They inhibit bacterial RNA polymerase.

**Indications**

Tuberculosis (TB) with other drugs
Selected serious or prosthesis-associated infection with other anti-staphylococcal agents
MRSA infection, with oral sodium fusidate, after IV anti-staphylococcal treatment
Prophylaxis for close contacts of people with meningococcal disease, H. influenzae type b disease, Leprosy

**Contraindications**

Jaundice or severe hepatic impairment
Allergy to any rifamycin derivative

**Specific considerations**

Treatment with ritonavir and saquinavir: combination of ritonavir-boosted saquinavir and rifampicin caused hepatitis in healthy volunteers; combination not recommended.

Hepatic impairment: Introduce rifampicin in stepwise fashion up to full doses if no adverse effects occur. Avoid rifamycins in severe impairment. Using other hepatotoxic drugs with rifampicin may increase the risk of further damage.

Pregnancy: Bleeding attributable to hypoprothrombinaemia has been reported in newborn infants and in mothers after the use of rifamycins during late pregnancy. If used during the last few weeks of pregnancy, vitamin K (phytomenadione) should be given to the mother and the newborn infant.

Breastfeeding: Rifampicin may be used; no data for rifabutin, avoid use.

**Adverse effects**

Common: self-limited flushing and itching (unrelated to an allergy), transient GI symptoms, orange–red colouration of body fluids, staining of soft contact lenses
Infrequent: wheeze, allergic reactions (see Allergy), cholestatic jaundice, hepatotoxicity (more common with intermittent doses and more likely if isoniazid is also used), blood dyscrasias (thrombocytopenia, neutropenia)
Rare: neurological symptoms, pseudomembranous colitis, thrombophlebitis (IV)

Allergy: Allergic reactions are infrequent and range from rash, flu-like syndrome and eosinophilia to haemolytic anaemia, haemoglobinuria and acute renal failure. It is more likely if doses are taken irregularly or intermittently, or if restarted after an interval without treatment. Patients taking rifampicin oral liquid may have an allergy to the preservative, sodium metabisulfite.

**Dosage**

Oral and IV dosage is the same.

**Tuberculosis:** Use as part of a multi-drug regimen.

**Adult, child**

Daily regimen, 10 mg/kg (maximum 600 mg) daily.
Three times a week regimen, 15 mg/kg (maximum 600 mg) 3 times each week.
Twice a week regimen, 15 mg/kg (maximum 900 mg) twice a week.
Staphylococcal infection: Adult, 600 mg daily in divided doses with another anti-staphylococcal agent. Child, 10–20 mg/kg daily in 1–2 doses with another anti-staphylococcal agent.
Leprosy: Paucibacillary, multibacillary, 600 mg once each month as part of multi-drug regimen.
Single skin lesion paucibacillary, 600 mg single dose with ofloxacin and minocycline

**H. influenzae type b prophylaxis:** Neonates, oral, 10 mg/kg daily for 4 days. Infants, children, adults, oral, 20 mg/kg (maximum 600 mg) daily for 4 days.

**N. meningitidis prophylaxis:** Neonates, oral, 5 mg/kg every 12 hours for 2 days. Infants, children, adults, oral 10 mg/kg every 12 hours (maximum 600 mg/dose) for 2 days.

**Patient counselling**

Rifampicin is absorbed best if you take it at least half an hour before food.

Your urine, faeces, sweat and tears may become an orange–red colour and soft contact lenses may become permanently stained.
Tell your doctor if you have any loss of appetite, nausea, vomiting, unusual fatigue, jaundice, dark urine or pale faeces. Take medication regularly, as stop–start dosing can cause flu-like illnesses. This medicine interacts with many drugs; tell your doctor and pharmacist that you are taking this medicine before starting or stopping any medicines, including herbal and over-the-counter products. Combined oral contraceptives During short term use (e.g. 2 days) of rifampicin, take an active pill daily during the course and for 7 days after last rifampicin dose and use extra contraceptive precautions, e.g. abstinence or a barrier method, continuing this for 4 weeks after the last rifampicin dose. During long term use of rifampicin, e.g. for tuberculosis, choose another contraceptive method and continue for at least 4 weeks after treatment stops. **Practice points**  - measure serum creatinine and full blood count before treatment  - monitor liver function tests each month if there is pre-existing liver impairment, or immediately if symptoms of hepatic toxicity occur; symptomatic rises in AST of up to 3–5 times upper limit of normal (providing patient is asymptomatic and not jaundiced) may be tolerated before stopping treatment  - rifampicin with pyrazinamide is not recommended for treatment of latent tuberculosis due to the increased risk of hepatic injury (combination is acceptable for treating active tuberculosis)  - rifampicin is bactericidal but resistance develops rapidly if used as sole agent  - use rifabutin rather than rifampicin in patients with HIV on combination antiretroviral therapy; treatment is complicated by drug interactions between antiretroviral drugs and rifampicin **Products**  - RIFAMPICIN CAPS 150 MG (RIFADIN®, RIFARAM®)  - RIFAMPICIN CAPS 300 MG (RIFADIN®, RIFARAM®, RIFASYNT®)  - RIFAMPICIN SYRUP. 100 MG/5ML  60 ML BOTTLE (RIFADIN®)  - RIFAMPICIN+ISONIAZIDE TABS 300+150 MG (RIFINAH®) **STREPTOMYCYIN** **Mode of action** Inhibit protein synthesis by irreversibly binding to the 30S ribosomal sub-unit and causing cell membrane damage. **Concentration-dependent bactericidal effect.** **Indications** Infections due to M. tuberculosis, M. kansasii where the strain is resistant to other antitubercular drugs or when other antitubercular drugs are contraindicated, Plague, Tularaemia, Brucellosis, Serious enterococcal infection with high level gentamicin (but not streptomycin) resistance **Contraindications** Serious allergy to streptomycin **Specific considerations** Vestibular disturbances, impaired hearing: ototoxicity is more likely to occur. Myasthenia gravis: streptomycin has neuromuscular blocking activity. Renal impairment: Avoid use in severe impairment. Elderly: Use reduced dose. Ototoxic and nephrotoxic effects may be more severe in the elderly. Pregnancy: congenital hearing loss has occurred; risk is low with careful dosing and limited duration of treatment; ADEC category D. Breastfeeding: Safe to use. **Adverse effects** The risk of adverse effects increases with cumulative doses >100 g. Common: fever, rash, sterile abscess at injection site. Infrequent: numbness around mouth, tinnitus, vestibular toxicity, high frequency range hearing impairment, urinary casts, albuminuria Rare: anaphylactic shock, exfoliative dermatitis, proximal tubular necrosis, agranulocytosis, aplastic anaemia **Dosage** Dose is expressed in terms of streptomycin base. Adult: IM (rarely IV), 15 mg/kg (maximum 1 g) daily, reducing to 2–3 times each week depending on progress. Maximum daily dose in people weighing <50 kg is 500–750 mg. Child: IM, 15 mg/kg (maximum 1 g) daily.
Elderly: IM, 10 mg/kg (maximum 500–750 mg) daily.
Renal impairment: Use normal dose but increase interval between doses so that trough concentration is not >5 micrograms/mL.

Concentration monitoring
To avoid increased risk of toxicity, trough concentration should not exceed 5 micrograms/mL.

Practice points
- monitor renal function
- audiometric and vestibular function should be assessed before treatment, every 2–3 months during treatment, and if auditory or vestibular symptoms develop; consider stopping treatment if ototoxicity is detected

Products
STREPTOMYCIN VIAL 1 GM/VIAL (NOT REGISTERED)

05.01.11 Metronidazole and tinidazole

METRONIDAZOLE

Mode of action
Metronidazole has no significant activity against aerobic or facultatively anaerobic bacteria. The antimicrobial properties of metronidazole stem from the reduction of its nitrogroup by bacterial nitroreductase, thereby producing cytotoxic compounds that disrupts the host DNA.

Indications
Metronidazole is an alternative to a penicillin for the treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes. It is the drug of first choice for the treatment of acute necrotising ulcerative gingivitis (Vincent’s infection) and pericoronitis. Gram-positive and Gram-negative anaerobic bacterial infections, e.g. B. fragilis. Protozoal infections, e.g. giardiasis, trichomoniasis. Pseudomembranous colitis (C. difficile). Dental infections, including acute gingivitis. Intra-abdominal infections, Aspiration pneumonia, Lung abscess, Bacterial vaginosis. Pelvic inflammatory disease, Amoebiasis (intestinal and extra-intestinal), Surgical prophylaxis. Eradication of H. pylori (as part of a multi-drug regimen).

Contraindications
Serious allergic reaction to metronidazole or tinidazole.

Specific considerations
Treatment with disulfiram: combination may cause psychotic reactions; do not use metronidazole within 2 weeks of disulfiram.
Treatment with fluorouracil: avoid combination (increases fluorouracil toxicity).
History of CNS disorders (including seizures): nitroimidazoles are neurotoxic and may aggravate existing neurological disease.
History of blood dyscrasias: may cause leucopenia.
Renal impairment: Metabolites may accumulate in severe impairment, causing adverse effects. Dose adjustment is not usually necessary.
Hepatic impairment: Risk of drug accumulation and toxicity in severe impairment; reduce dosage.
Pregnancy: Safe to use, take in divided doses if possible; ADEC category B2.
Breastfeeding: Safe to use. May cause some bitterness in milk. Use in divided doses given after breastfeeding rather than single daily doses.

Adverse effects
Common: nausea, diarrhoea, metallic taste, thrombophlebitis (IV)
Infrequent: hypersensitivity reactions (rash, itch, flushing, fever), headache, dizziness, vomiting, glossitis, stomatitis, dark urine, paraesthesia
Rare: pancreatitis, hepatitis, optic neuritis, peripheral neuropathy, seizures, anaphylactic shock and angioedema
High dose and/or prolonged treatment (>10 days): furry black tongue, leucopenia, neutropenia, increased risk of peripheral neuropathy and/or CNS toxicity

Dosage
Adult
Oral, 200–400 mg every 8–12 hours, up to 4 g daily.
Rectal, 1 g every 8–12 hours.
Child
Oral/IV, 7.5 mg/kg every 8 hours.
Rectal, 1–5 years, 250 mg 3 times daily.
Rectal, 6–12 years, 500 mg 3 times daily.
Severe infections, e.g., septicemia, acute peritonitis, aspiration pneumonia, PID
IV, 500 mg every 8–12 hours as part of multi-drug regimen. Maximum 4 g daily.
Pseudomembranous colitis
Adult, oral, 400 mg every 8 hours for 7–10 days.
Child, oral, 10 mg/kg every 8 hours for 7–10 days.
Surgical prophylaxis
Adult
IV, 500 mg ending infusion at time of induction.
Rectal, 1 g as a single dose 8 hours before surgery.
Oral, 400 mg as a single dose 1–2 hours before surgery.
Child
IV, 12.5 mg/kg (maximum 500 mg) ending infusion at time of induction.
Acute intestinal amebiasis
Treatment course can be repeated after 2 weeks if necessary.
Adult, oral, 600–800 mg every 8 hours for 6–10 days followed by paromomycin.
Child, oral, 15 mg/kg every 8 hours (maximum 800 mg every 8 hours) for 6–10 days followed by paromomycin.
Extra-intestinal amebiasis (liver abscess)
Aspiration of liver abscess may be required; seek specialist advice.
Adult, oral, 600–800 mg every 8 hours for 10–14 days followed by paromomycin.
Child, oral, 15 mg/kg every 8 hours (maximum 800 mg every 8 hours) for 10–14 days followed by paromomycin.
Bacterial vaginosis
Oral, 400 mg twice daily for 5 days.
Trichomoniasis
Adult, oral, 2 g single dose; or, if this fails, 400 mg twice daily for 5 days. Use the 5-day course in pregnancy and breastfeeding. Treat sexual partner(s) as well.
Giardiasis
Adult, oral, 2 g daily for 3 days; or, if this fails, 400 mg every 8 hours for 7 days. Use the 7-day course in pregnancy and breastfeeding.
Child, oral, 30 mg/kg once daily (maximum 2 g) for 3 days or, if this fails, 10 mg/kg 3 times a day for 7 days.
Eradication of H. pylori
With clarithromycin, oral, 400 mg twice daily for 7 days.
With amoxycillin, oral, 400 mg 3 times daily for 14 days.
Severe hepatic impairment: Oral/IV, halve usual dose.
Administration instructions
Give IV infusion over 15–30 minutes.
Patient counseling
Take metronidazole tablets with food to reduce stomach upset.
Metronidazole liquid is absorbed best if taken 1 hour before food.
Avoid alcohol during treatment and for 24 hours after finishing the course to prevent nausea, vomiting, flushing, headache and palpitations (sometimes occur when alcohol is taken with metronidazole).
Stop taking metronidazole and check with your doctor immediately if you have any numbness, tingling, pain or weakness in hands or feet.
Practice points
• for indications where the dosing frequency is given as the range ‘every 8–12 hours’ there is little published evidence to support dosing every 12 hours, although it is commonly used in Australia
• good oral (100%) and rectal (60–80%) bioavailability; convert from IV to oral treatment as soon as possible; IV route can be avoided in some infections
• rectal dosing results in a systemic concentration similar to oral dosing
• oral absorption from suspension is lower than from tablets
• H. pylori resistance to metronidazole reduces the efficacy of combined regimens; about 50% of H. pylori strains in adults are resistant
• monitor blood count and neurotoxic reactions when treating for >10 days
• most active of the available bactericidal drugs for Gram-positive and Gram-negative anaerobes
• inactive against aerobic and facultative anaerobic bacteria
• therapeutic CNS concentrations are achieved with oral dosing
• metronidazole and tinidazole are relatively ineffective for treating asymptomatic passers of Entamoeba histolytica cysts as they are almost completely absorbed and little active drug remains in the GIT
• metronidazole is more suitable for children as an oral liquid is available

**Products**

**METRONIDAZOLE SUSP. 125 MG/5ML 100 ML BOTTLE** (METROZOLE®, NIDAZOLE®, PROTOZOL®, RAMZOL®)

**METRONIDAZOLE TABS 250 MG** (DUMOZOL®, ENTOGYL®, FLAGYL®, FLANIZOL®, METROLAG®, METROZOLE®, NIDAZOLE®, PROTOZOL®, RAMAZOL®, SUPPLIN®)

**METRONIDAZOLE TABS 500 MG** (DUMOZOL®, FLAGYL®, FLANIZOL®, METROLAG®, METROZOLE®, NIDAZOLE®, RAMAZOL®, SUPPLIN®)

**METRONIDAZOLE VAGINAL SUPP. 500 MG** (ELYZOL®, FLAGYL®, METRAZIN®, METROZOLE®)

**METRONIDAZOLE VIAL 5 MG/ML 100 ML VIAL** (EFLARON®, FLAGYL®, METRONIDAZOL®, NIDAZOLE®, SUPPLIN®)

**TINIDAZOLE**
Tinidazole is similar to metronidazole but has a longer duration of action

**Mode of action**
Same as Metronidazole.

**Indications**
Gram-positive and Gram-negative anaerobic bacterial infections, eg *B. fragilis*
Protozoal infections, eg giardiasis, trichomoniiasis
Amoebiasis (intestinal and extra-intestinal)
Prophylaxis in GI and gynaecological surgery

**Contraindications**
Same as Metronidazole.

**Specific considerations**
History of CNS disorders (including seizures): nitroimidazoles are neurotoxic and may aggravate existing neurological disease.
History of blood dyscrasias: may cause leucopenia
Renal impairment: Renally excreted but no dose adjustment required for short course treatment.
Pregnancy: Safe to use; use in divided doses rather than single dose; ADEC category B3.
Breastfeeding: Use metronidazole in preference; use in divided doses rather than single dose.

**Adverse effects**
Same as Metronidazole

**Dosage:**
2 g as a single dose.
Surgical prophylaxis: Adult, 2 g 6–12 hours before surgery.
Giardiasis, trichomoniasis
Adult
2 g single dose. Give divided doses in pregnancy.
For trichomoniiasis treat sexual partner(s).
Child
50 mg/kg (maximum 2 g) single dose. May need to repeat after 24–48 hours.
Acute intestinal amoebiasis
Follow course by paromomycin
Adult, 2 g daily for 3 days.
Child, 50 mg/kg (maximum 2 g) daily for 3 days.
If treatment fails give tinidazole for 10 days.
Extra-intestinal amoebiasis (liver abscess)
Aspiration of liver abscess may be required.
Follow course by paromomycin.
Adult, 2 g daily for 3–5 days.
Child, 50 mg/kg (maximum 2 g) daily for 5 days.

**Patient Counselling**
Take with food to reduce stomach upset.

**Practice points**
- monitor blood count and neurotoxic reactions when treating for >10 days
- most active of the available bactericidal drugs for Gram-positive and Gram-negative anaerobes
- inactive against aerobic and facultative anaerobic bacteria
- therapeutic CNS concentrations are achieved with oral dosing
- metronidazole and tinidazole are relatively ineffective for treating asymptomatic passers of *Entamoeba histolytica* cysts as they are almost completely absorbed and little active drug remains in the GIT
- metronidazole is more suitable for children as an oral liquid is available

**Products**
TINIDAZOLE TABS 500 MG (FASIGYN®, PROTOGYN®, SPORINEX®, TINAZOL®)

**05.01.12 Quinolones**

Nalidixic acid is effective in uncomplicated urinary-tract infections. Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as Streptococcus pneumoniae and Enterococcus faecalis; it should not be used for pneumococcal pneumonia. It is active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Uses for ciprofloxacin include infections of the respiratory tract (but not for pneumococcal pneumonia) and of the urinary tract, and of the gastro-intestinal system (including typhoid fever), and gonorrhoea and septicaemia caused by sensitive organisms.

Levofloxacin is active against Gram-positive and Gram-negative organisms. It has greater activity against pneumococci than ciprofloxacin. Levofloxacin is licensed for community-acquired pneumonia but it is considered to be second-line treatment for this indication. Although ciprofloxacin, levofloxacin and ofloxacin are licensed for skin and soft-tissue infections, many staphylococci are resistant to the quinolones and their use should be avoided in MRSA infections. Moxifloxacin should be used for treating acute exacerbations of chronic bronchitis only if conventional treatment has failed or is contra-indicated, and for second-line treatment of community-acquired pneumonia. Moxifloxacin is active against Gram-positive and Gram-negative organisms. It has greater activity against Gram-positive organisms including pneumococci than ciprofloxacin. Moxifloxacin is not active against Pseudomonas aeruginosa or meticillin-resistant Staphylococcus aureus (MRSA).

**Anthrax**

Inhalation or gastro-intestinal anthrax should be treated initially with either ciprofloxacin or doxycycline [unlicensed indication] combined with one or two other antibacterials (such as amoxicillin, benzylpenicillin, chloramphenicol, clarithromycin, clindamycin, imipenem with cilastatin, rifampicin [unlicensed indication], and vancomycin). When the condition improves and the sensitivity of the Bacillus anthracis strain is known, treatment may be switched to a single antibacterial. Treatment should continue for 60 days because germination may be delayed. Cutaneous anthrax should be treated with either ciprofloxacin [unlicensed indication] or doxycycline [unlicensed indication] for 7 days. Treatment may be switched to amoxicillin if the infecting strain is susceptible. Treatment may need to be extended to 60 days if exposure is due to aerosol. A combination of antibacterials for 14 days is recommended for cutaneous anthrax with systemic features, extensive oedema, or lesions of the head or neck. Ciprofloxacin or doxycycline may be given for post-exposure prophylaxis. If exposure is confirmed, antibacterial prophylaxis should continue for 60 days. Antibacterial prophylaxis may be switched to amoxicillin after 10–14 days if the strain of B. anthracis is susceptible. Vaccination against anthrax may allow the duration of antibacterial prophylaxis to be shortened.

**Cautions**

Quinolones should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures, in G6PD deficiency, myasthenia gravis (risk of exacerbation), in renal impairment, pregnancy, during breast-feeding, and in children or adolescents (arthropathy has developed in weight-bearing joints in young animals). Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). The CSM has warned that
quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them.

**Use in children**
Quinolones cause arthropathy in the weight-bearing joints of immature animals and are therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of a quinolone in children may be justified. Nalidixic acid is used for urinary-tract infections in children over 3 months of age. Ciprofloxacin is licensed for pseudomonal infections in cystic fibrosis (for children above 5 years of age), and for treatment and prophylaxis of inhalational anthrax.

**CSM advice (tendon damage)**
Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment. The CSM has reminded that:
- quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use;
- elderly patients are more prone to tendinitis;
- the risk of tendon rupture is increased by the concomitant use of corticosteroids;
- if tendinitis is suspected, the quinolone should be discontinued immediately.

**CIPROFLOXACIN**

**Mode of action**
Bactericidal; inhibit bacterial DNA synthesis by blocking DNA gyrase and topoisomerase IV.

**Indications**
Severe salmonella enteritis, typhoid and paratyphoid (enteric fever), Shigellosis, gonorrhoea, Complicated UTIs, Bone or joint infections, Epididymo-orchitis, Meningococcal prophylaxis
P. aeruginosa infections, e.g. in cystic fibrosis, Prostatitis, Febrile neutropenia (follow-up treatment in low risk patients, with amoxycillin with clavulanic acid)

**Contraindications**
Serious allergic reaction to quinolones

**Specific considerations**
Epilepsy, history of CNS disorders: may induce seizures.
Treatment with bupropion: may increase risk of seizures; avoid combination.
Myasthenia gravis: may exacerbate symptoms.
G6PD deficiency: increase risk of haemolytic anaemia.
Prior or concomitant use of corticosteroids: increase risk of tendon damage.
Renal impairment: Reduce dose in moderate-to-severe impairment.
Elderly: Increased risk of tendon damage.
Children: Use in children is controversial as quinolones induce arthropathy in immature animals. Although damage to growing cartilage has not been demonstrated in humans, quinolones are recommended for use in children and adolescents only in severe infections where benefit outweighs the risk of arthropathy, eg febrile neutropenia, P. aeruginosa infections in cystic fibrosis.

**Pregnancy:** Quinolones best avoided in pregnancy due to potential for fetal arthropathy; ADEC category B3.

**Breastfeeding:** Use alternatives when possible. Contact specialised information service. Short courses may be acceptable in some circumstances.

**Adverse effects**
Common: rash, nausea, vomiting, diarrhoea, abdominal pain, dyspepsia
Infrequent: headache, dizziness, insomnia, depression, restlessness, tremors, arthralgia, arthritis, myalgia, tendonitis, crystalluria, interstitial nephritis, raised liver enzymes, erythema, itch, pain or thrombophlebitis at IV infusion site
Rare: hypoglycaemia, hyperglycaemia, blood dyscrasias, convulsions, psychotic reactions, phototoxicity, angioedema, anaphylaxis, pseudomembranous colitis, tendon rupture, hepatitis, peripheral neuropathy Stevens–Johnson syndrome, fixed drug eruption, changes in vision, pancytopenia

**Dosage**
**Adult:** Oral, 250–500 mg twice daily. Maximum 1.5 g daily. IV, 200–300 mg twice daily. Maximum 1200 mg daily.
Severe infections: IV, 300–400 mg every 8–12 hours.
Bone and joint infections: Oral, 750 mg twice daily.
N. meningitidis prophylaxis: Oral, 500 mg as a single dose.
Gonococcal infection (beta-lactamase producing N. gonorrhoea): Oral, 500 mg as a single dose. Add doxycycline or azithromycin if in a high risk (presumptive treatment for Chlamydia and other non-gonococcal genital infections) group. See AZITHROMYCIN, DOXYCYCLINE.
Enteric fever (typhoid or paratyphoid): 500 mg orally twice daily for 14 days; or 400 mg IV every 12 hours. Change to oral route as soon as possible.

Moderate-to-severe renal impairment: 250–500 mg oral daily; or 200–400 mg IV daily.

Child: Oral/IV, 5–10 mg/kg every 12 hours.

Cystic fibrosis: Oral, 15 mg/kg (maximum 750 mg) every 12 hours.

**Administration instructions**

Give IV infusion over at least 60 minutes (to minimise local reactions).

**Patient counselling**

Ciprofloxacin is absorbed best if you take it 1 hour before, or 2 hours after, meals.

Dairy products, antacids, iron, zinc or calcium supplements may interfere with the absorption of ciprofloxacin; do not take them within 2 hours of a dose of ciprofloxacin.

It may increase the effects of caffeine in some people; you may need to reduce your caffeine intake.

Avoid sun exposure, wear protective clothing and use sunscreen.

Drink plenty of fluids while taking this medicine.

This medicine may cause dizziness or faintness which can affect your ability to drive and/or operate machinery.

Drinking alcohol may worsen these effects.

Stop taking this medicine, don't exercise, and see your doctor as soon as possible if you have any tendon soreness or inflammation.

**Practice points**

- excellent tissue penetration into bone and fluids, except CSF
- well absorbed orally; IV route necessary only when oral administration is not possible
- reduced sensitivity of S. typhi has been associated with typhoid fever treatment failures
- quinolones have very limited use in general practice, except in the treatment of UTIs caused by resistant organisms, or when other agents are contraindicated
- cases of quinolone-resistant N. gonorrhoeae are becoming widespread in parts of Asia, limiting the role of quinolones in treating gonorrhoea
- stop quinolone treatment at first sign of tendon pain or inflammation
- superinfection with enterococci or Candida species may occur
- ensure adequate fluid intake and urine output; avoid excessively alkaline urine due to risk of crystalluria

**Products**

- CIPROFLOXACIN TABS 250 MG (BACTALL®, CIFRAN®, CIPROBAY®, CIPRODAR®, CIPROFLOX®, CIPROMID®, CIPROPHARM®, CIPROQUIN®, FLOXIN®, RIVROXIN®)
- CIPROFLOXACIN TABS 500 MG (FLOXIN®, BACTALL®, CIPRO®, CIPROBAY®, CIPRODAR®, CIPROMID®, CIPROPHARM®, CIPROQUIN®, FLOXIN®, RIVROXIN®)
- CIPROFLOXACIN VIAL INFUSION 2 MG/ML 100 ML VIAL (CIPROBAY®, CIPROFLOX®, CIPROLOX®, UFEXIL®, RIVROXIN®)

**LEVOFLOXACIN**

**Mode of action**

Same as Ciprofloxacin.

**Indications**

Levofloxacin is generally considered to be about twice as active as its isomer, ofloxacin. It has a broad spectrum of activity which includes Gram-positive bacteria.

**Contraindications**

Same as Ciprofloxacin

**Specific Considerations**

- Epilepsy, history of CNS disorders: may induce seizures.
- Treatment with bupropion: may increase risk of seizures; avoid combination.
- Myasthenia gravis: may exacerbate symptoms.
- G6PD deficiency: increase risk of haemolytic anaemia.
- Prior or concomitant use of corticosteroids: increase risk of tendon damage.
- Elderly: Increased risk of tendon damage.
Children: Use in children is controversial as quinolones induce arthropathy in immature animals. Although damage to growing cartilage has not been demonstrated in humans, quinolones are recommended for use in children and adolescents only in severe infections where benefit outweighs the risk of arthropathy, eg febrile neutropenia, P. aeruginosa infections in cystic fibrosis.

Pregnancy: Quinolones best avoided in pregnancy due to potential for fetal arthropathy; ADEC category B3.

Breastfeeding: Use alternatives when possible. Contact one of the pregnancy drug information centres. Short courses may be acceptable in some circumstances.

**Adverse Effects**

As for Ciprofloxacin.

Additionally, Levofloxacin has been found in isolated cases to prolong the QT interval, particularly in overdosage.

**Interactions**

Same as Ciprofloxacin

**Dosage**

It is given by mouth or intravenously for the treatment of susceptible infections in a usual dose of 250 or 500 mg once or twice daily. A regimen of 750 mg once daily is recommended in the USA for complicated skin infections and for hospital-acquired pneumonia. Doses should be reduced in patients with renal impairment. Levofloxacin is also used topically as 0.5% eye drops for the treatment of bacterial conjunctivitis.

Renal impairment.

Although initial doses remain unchanged in patients with renal impairment, subsequent doses of levofloxacin should be reduced according to creatinine clearance (CC):

- CC 20 to 50 mL/minute: subsequent doses are halved
- CC 10 to 19 mL/minute: subsequent doses are reduced to one-quarter of the standard dose (a regimen of 250 mg daily should be reduced to 125 mg every other day)
- CC less than 10 mL/minute: standard doses of 250 mg or 500 mg daily are reduced to 125 mg every 48 or 24 hours respectively; a regimen of 500 mg twice daily is reduced to 125 mg every 24 hours

**Patient counselling**

- Drink plenty of fluids while taking this medicine.
- This medicine may cause dizziness or faintness which can affect your ability to drive and/or operate machinery.
- Drinking alcohol may worsen these effects.
- Stop taking this medicine, don't exercise, and see your doctor as soon as possible if you have any tendon soreness or inflammation.

**Practice points**

- quinolones have very limited use in general practice, except in the treatment of UTIs caused by resistant organisms, or when other agents are contraindicated
- cases of quinolone-resistant N. gonorrhoeae have been reported in Australia and are becoming widespread in parts of Asia, limiting the role of quinolones in treating gonorrhoea
- stop quinolone treatment at first sign of tendon pain or inflammation
- superinfection with enterococci or Candida species may occur
- ensure adequate fluid intake and urine output; avoid excessively alkaline urine due to risk of crystalluria

**Products**

- LEVOFLOXACIN TABS 500 MG (TAVANIC®)
- LEVOFLOXACIN VIAL 5 MG/ML 100 ML VIAL (TAVANIC®)

**MOXIFLOXACIN**

**Mode of action**

Bactericidal; inhibit bacterial DNA synthesis by blocking DNA gyrase and topoisomerase IV.

**Indications**

- Severe community-acquired pneumonia (adult)
- Acute bacterial sinusitis where other treatments have failed or are contraindicated (adult)
- Acute exacerbations of chronic bronchitis where other treatments have failed or are contraindicated (adult)
- Severe mixed aerobic and anaerobic infections (as a single agent) especially if an aminoglycoside-containing regimen is contraindicated
- Multi-drug resistant tuberculosis

**Contraindications**

- Prolongation of QT interval, or treatment with drugs which may prolong QT interval
- Serious allergic reaction to quinolones, including nalidixic acid
Specific considerations
Risk factors for prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
Epilepsy, history of CNS disorders: may induce seizures.
Treatment with bupropion: may increase risk of seizures; avoid combination.
Myasthenia gravis: may exacerbate symptoms.
G6PD deficiency: increase risk of haemolytic anaemia.
Prior or concomitant use of corticosteroids—increase risk of tendon damage.
Elderly: Increased risk of tendon damage.
Children: Use in children is controversial as quinolones induce arthropathy in immature animals. Although damage to growing cartilage has not been demonstrated in humans, quinolones are recommended for use in children and adolescents only in severe infections where benefit outweighs the risk of arthropathy, eg febrile neutropenia, P. aeruginosa infections in cystic fibrosis.
Pregnancy: Quinolones best avoided in pregnancy due to potential for fetal arthropathy; ADEC category B3.
Breastfeeding: Use alternatives when possible.. Short courses may be acceptable in some circumstances.

Adverse effects
Common: rash, itch, nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, dizziness, injection site reaction, taste change
Infrequent: headache, dizziness, insomnia, depression, restlessness, tremors, arthralgia, arthritis, myalgia, tendonitis, crystalluria, interstitial nephritis, raised liver enzymes, QT prolongation, ventricular tachyarrhythmias, torsades de pointes, cardiac arrest, palpitations
Rare: hypoglycaemia, hyperglycaemia, blood dyscrasias, seizures, psychotic reactions, angioedema, anaphylaxis, pseudomembranous colitis, tendon rupture, Stevens–Johnson syndrome, hepatitis, peripheral neuropathy, Stevens–Johnson syndrome

Dosage
Acute bacterial sinusitis
Oral, 400 mg once daily for 10 days.
Community-acquired pneumonia
Oral/IV, 400 mg once daily for 7–14 days.
Acute bacterial exacerbation of chronic bronchitis
Oral/IV, 400 mg once daily for 5 days.

Administration instructions
Administer IV over 60 minutes; avoid bolus or rapid infusion.

Patient counselling
Antacids, iron or zinc supplements may interfere with the absorption of moxifloxacin; do not take them within 2 hours of a dose of moxifloxacin.
Tell your doctor if you have any palpitations or fainting spells while taking moxifloxacin.
Drink plenty of fluids while taking this medicine.
This medicine may cause dizziness or faintness which can affect your ability to drive and/or operate machinery.
Drinking alcohol may worsen these effects.
Stop taking this medicine, don't exercise, and see your doctor as soon as possible if you have any tendon soreness or inflammation.

Practice points
• dosage remains the same when changing between IV and oral routes
• moxifloxacin has no advantage over ciprofloxacin in the treatment of most Gram-negative infections
• quinolones have very limited use in general practice, except in the treatment of UTIs caused by resistant organisms, or when other agents are contraindicated
• moxifloxacin may be used to treat severe Legionella pneumonia and severe community-acquired pneumonia, especially if penicillin resistance is suspected or the patient is allergic to penicillin
• cases of quinolone-resistant N. gonorrhoeae have been reported in Australia and are becoming widespread in parts of Asia, limiting the role of quinolones in treating gonorrhoea
• stop quinolone treatment at first sign of tendon pain or inflammation
• superinfection with enterococci or Candida species may occur
• ensure adequate fluid intake and urine output; avoid excessively alkaline urine due to risk of crystalluria
NALIDIXIC ACID

Mode of action
Nalidixic acid is considered to act by interfering with the replication of bacterial DNA, probably by inhibiting DNA gyrase (topoisomerase) activity. Bacterial resistance may develop rapidly, sometimes within a few days of commencing treatment, but it does not appear to be transferable or R-plasmid mediated. Cross-resistance occurs with oxolinic acid and cinoxacin. The antibacterial activity of nalidixic acid is not significantly affected by differences in urinary pH. Antagonism between nitrofurantoin and nalidixic acid has been demonstrated in vitro.

Indications:
treatment of uncomplicated lower urinary-tract infections due to Gram-negative bacteria other than Pseudomonas spp. It has also been used to treat shigellosis (bacillary dysentery).

Contraindications
Allergy to Quinolones
Nalidixic acid should be avoided in patients subject to convulsions.

Specific considerations
It should be given with care to patients with renal or hepatic impairment, severe cerebral arteriosclerosis, or G6PD deficiency. Blood counts and renal and hepatic function should be monitored if treatment continues for more than 2 weeks.

It should be avoided in infants less than 3 months old. Since nalidixic acid and related antimicrobials have been shown to cause degenerative changes in weight-bearing joints of young animals, it has been suggested that these compounds should not be used in children, adolescents, pregnant women, or during breast feeding.

Exposure to strong sunlight or sunlamps should be avoided during treatment with nalidixic acid.

Nalidixic acid may cause false-positive reactions in urine tests for glucose using copper reduction methods.

Nalidixic acid is reported to enhance the effect of oral anticoagulants such as warfarin; this may be due in part to displacement of anticoagulant from its plasma binding sites. The dose of anticoagulant may need to be reduced.

Adverse Effects
The most frequent adverse reactions to nalidixic acid involve the gastrointestinal tract, skin, and CNS.
Gastrointestinal effects have been reported in about 8% of patients and include nausea, vomiting, diarrhoea, and abdominal pain.
Neurological effects include visual disturbances, headache, dizziness or vertigo, drowsiness, and sometimes confusion, depression, excitement, and hallucinations. Toxic psychoses or convulsions have occurred, especially after large doses; convulsions are most likely in patients with predisposing factors such as cerebrovascular insufficiency, parkinsonism, or epilepsy. There have been reports of intracranial hypertension, especially in infants and young children, and also of metabolic acidosis. Peripheral neuropathies, muscular weakness, and myalgia are occasional adverse effects. Sixth cranial nerve palsy has been reported rarely.

Adverse effects on the skin include photosensitivity reactions with erythema and bullous eruptions, allergic rashes, urticaria, and pruritus. Erythema multiforme and Stevens-Johnson syndrome have been reported rarely. Eosinophilia, fever, angioedema, and, rarely, anaphylactoid reactions have occurred. Arthralgia has been reported (degenerative changes in weight-bearing joints of young animals are documented). Tendon damage has occasionally been associated with related compounds, the fluoroquinolones.

Cholestatic jaundice, thrombocytopenia, and leucopenia have occurred rarely, as has haemolytic anaemia in patients who may or may not have G6PD deficiency. There have been isolated reports of fatal autoimmune haemolytic anaemia in elderly patients.

Fatal haemorrhagic enterocolitis has been associated with the use of nalidixic acid and high-dose intravenous melphalan in children. There is a possible risk of increased nephrotoxicity when nalidixic acid is given with ciclosporin.

Dosage
The usual adult dose is 4 g daily by mouth in 4 divided doses for at least 7 days in acute infections, reducing to half this dose in chronic infections. Since bacterial resistance may develop rapidly it has been suggested that if treatment with nalidixic acid has not resulted in a negative urine culture within 48 hours another antimicrobial should be used.
Children over 3 months have been given 50 to 55 mg/kg daily in 4 divided doses reduced to 30 to 33 mg/kg daily for prolonged treatment.
Although the antibacterial activity of nalidixic acid does not appear to be influenced by urinary pH, the use of sodium bicarbonate or sodium citrate does increase the concentration of active drug in the urine. The adult dose of nalidixic acid, in conjunction with sodium citrate, is 660 mg three times daily for 3 days.

**Practice points**
- The excretion of nalidixic acid is reduced and plasma concentrations increased by probenecid
- Nitrofurantoin and nalidixic acid are antagonistic in vitro and should not be used together

**Products**
NALIDIXIC ACID TABS 500 MG (NALIDIX®)

**05.02 ANTIFUNGAL DRUGS**

**TREATMENT OF FUNGAL INFECTIONS**

**Aspergillosis**
Aspergillosis most commonly affects the respiratory tract but in severely immunocompromised patients, invasive forms can affect the sinuses, heart, brain, and skin. Voriconazole is the drug of choice; amphotericin (liposomal formulation preferred if toxicity or renal impairment are concerns) and itraconazole are alternatives in patients in whom initial treatment has failed. Itraconazole is also used as an adjunct in the treatment of allergic bronchopulmonary aspergillosis [unlicensed indication]. Caspofungin is licensed for invasive aspergillosis unresponsive to amphotericin or to itraconazole, or in patients who cannot tolerate amphotericin or itraconazole. The Scottish Medicines Consortium (March 2003) does not recommend the use of caspofungin because of a lack of robust data on efficacy and safety in the treatment of invasive aspergillosis.

**Candidiasis**
Many superficial candidal infections including infections of the skin are treated locally; widespread or intractable infection requires systemic antifungal treatment. Vaginal candidiasis may be treated with locally acting antifungals or with fluconazole given by mouth; for resistant organisms, itraconazole can be given by mouth. Oropharyngeal candidiasis generally responds to topical therapy; fluconazole is given by mouth for unresponsive infections; it is effective and is reliably absorbed. Itraconazole may be used for fluconazole-resistant infections. For deep and disseminated candidiasis, amphotericin by intravenous infusion is used alone or with flucytosine by intravenous infusion; an alternative is fluconazole given alone for Candida albicans infection, particularly in AIDS patients. Voriconazole is licensed for infections caused by fluconazole-resistant Candida spp. (including C. krusei). The use of caspofungin should be restricted to treating fluconazole-resistant Candida infections that have not responded to amphotericin or in patients intolerant of amphotericin.

**Cryptococcosis**
Cryptococcosis is uncommon but infection in the immunocompromised, especially in AIDS patients, can be life-threatening; cryptococcal meningitis is the most common form of fungal meningitis. The treatment of choice in cryptococcal meningitis is amphotericin by intravenous infusion with flucytosine by intravenous infusion for 2 weeks, followed by fluconazole by mouth for 8 weeks. In cryptococcosis, fluconazole given alone is an alternative in AIDS patients with no disturbances of consciousness. Following successful treatment, fluconazole can be used for prophylaxis against relapse until immunity recovers.

**Histoplasmosis**
Histoplasmosis is rare in temperate climates; it can be life-threatening, particularly in HIV-infected persons. Itraconazole can be used for the treatment of immunocompetent patients with indolent non-meningeal infection including chronic pulmonary histoplasmosis; ketoconazole is an alternative in immunocompetent patients. Amphotericin by intravenous infusion is preferred in patients with fulminant or severe infections. Following successful treatment, itraconazole can be used for prophylaxis against relapse.

**Skin and nail infections**
Mild localised fungal infections of the skin (including tinea corporis, tinea cruris, and tinea pedis) respond to topical therapy. Systemic therapy (itraconazole, fluconazole, or terbinafine) is appropriate if topical therapy fails, if many areas are affected, or if the site of infection is difficult to treat such as in infections of the nails (onychomycosis) and of the scalp (tinea capitis). Griseofulvin is used for tinea capitis in adults and children; it was used extensively in tinea of various other sites but it has largely been replaced by newer antifungals. Oral imidazole or triazole antifungals (particularly itraconazole) and terbinafine are used more commonly because they have a broader spectrum of activity and require a shorter duration of treatment. The role of terbinafine in the management of Microsporum species (cat or dog ringworm) is uncertain.
Pityriasis versicolor may be treated with itraconazole by mouth if topical therapy is ineffective; fluconazole by mouth is an alternative. Oral terbinafine is not effective for pityriasis versicolor. Terbinafine and itraconazole have largely replaced griseofulvin for the systemic treatment of onychomycosis, particularly of the toenail; terbinafine is considered to be the drug of choice. Itraconazole can be administered as intermittent 'pulse' therapy.

**Immunocompromised patients**

Immunocompromised patients are at particular risk of fungal infections and may receive antifungal drugs prophylactically; oral imidazole or triazole antifungals are the drugs of choice for prophylaxis. Fluconazole is more reliably absorbed than itraconazole and ketoconazole and is considered less toxic than ketoconazole on long-term use. Amphotericin by intravenous infusion is used for the empirical treatment of serious fungal infections. Fluconazole is used for treating Candida albicans infection. Caspofungin is licensed for the empirical treatment of systemic fungal infections (such as those involving Candida spp. or Aspergillus spp.) in patients with neutropenia.

**AMPHOTERICIN**

**Mode of action**

Polyene antifungal binds irreversibly to ergosterol in fungal cell membranes causing cell death by altering their permeability and allowing leakage of intracellular components.

**Indications**

Marketed: Severe systemic fungal infections, e.g. fungaemia, deep infections (conventional)

Drug of choice in cryptococcal meningitis (conventional)

Intolerance to conventional amphotericin (cholesteryl sulfate complex)

Prophylaxis of systemic candidiasis, aspergillosis and cryptococcosis following liver transplant (liposomal)

Treatment and suppression of oral and perioral candidiasis (conventional, lozenge)

Empirical treatment in high risk febrile neutropenic patients not responding to antibacterials (liposomal)

Visceral leishmaniasis (amphotericin, liposomal)

Accepted: Amoebic meningitis

**Contraindications**

Hypersensitivity to amphotericin, unless the condition is only amenable to treatment with amphotericin

**Specific considerations**

Pre-existing cardiac or pulmonary disease: poor tolerance of febrile reaction.

Where nephrotoxicity is especially undesirable: consider using a lipid formulation of amphotericin or other less nephrotoxic alternative to conventional amphotericin.

Treatment with nephrotoxic drugs (e.g. aminoglycosides, cyclosporin): may increase likelihood of renal impairment; avoid combination or monitor renal function closely.

Renal impairment: No dosage reduction necessary in impaired renal function, but further impairment may occur. If creatinine clearance falls (e.g. <30 mL/minute) while using conventional amphotericin continue with caution and consider increasing the dosing interval; or use one of the other formulations of amphotericin or alternative antifungal agent.

Children: Limited experience with amphotericin formulations apart from conventional, but doses comparable to those used for adults (on a mg/kg basis) have been used for them.

Pregnancy: Safe to use; ADEC category B3.

Breastfeeding: Oral, safe to use. IV, limited data; poor oral absorption by infant; unlikely to be of concern.

**Adverse effects**

Some adverse effects have different rates depending on the formulation used.

Common: IV, infusion reactions, thrombophlebitis, anaemia, reversible nephrotoxicity (see Nephrotoxicity)

Infrequent: Oral, mild nausea, vomiting, diarrhoea

IV, anuria, oliguria, hypotension, hypertension, cardiac arrest, torsades de pointes, blood dyscrasias, GI bleeding, rash, neurologic effects (e.g. seizure), acute hepatic failure, headache

Rare: anaphylactoid reaction

Nephrotoxicity: Conventional IV amphotericin affects renal function in all patients; changes are dose related and generally reversible (except when cumulative doses exceed 3–5 g). Nephrotoxicity from use of other amphotericin formulations is less frequent (see also Practice points).

Distal tubular damage may lead to loss of concentrating ability, renal tubular acidosis, hypokalaemia and hypomagnesaemia. Risk is greater in those with pre-existing renal impairment or use with other potentially nephrotoxic drugs.

Nephrotoxicity may be reduced by sodium loading (prehydration with 1 L sodium chloride 0.9% daily before IV
amphotericin if clinical status will allow sodium load). Administration of conventional amphotericin by continuous infusion reduces nephrotoxicity and infusion reactions. Infusion reactions: Include fever, chills, hypotension, anorexia, nausea, vomiting, headache, malaise, muscle and joint pain; usually lessen with continued treatment. One or more acute infusion reactions (chest pain, hypoxia, dyspnoea; severe abdominal, flank or leg pain; flushing and urticaria) may occur with liposomal amphotericin (AmBisome®); these may be related to the liposomal component; frequency is very variable.

**Dosage**

Use the same doses for adults and children.

Amphotericin, conventional, IV (Fungizone®): To minimise infusion-related reactions, infuse the initial dose slowly over 2–6 hours; alternatively, infuse the first 1 mg of the initial dose over 30 minutes, then give the remainder over 2–4 hours.

Systemic fungal infections: IV infusion 0.5–1 mg/kg daily, or according to specialist advice. Use 1 mg/kg/day for C. krusei, C. glabrata or mould infections. For prolonged treatment a higher dose may be given on alternate days; increase dose gradually every other day until this dose reached (maximum 1.5 mg/kg daily). Cumulative dose is usually in the order of 1–3 g (adults), depending on severity of infection and patient response. Mould infections (e.g. Aspergillus) usually require higher cumulative doses than yeast infections (e.g. Candida). Prophylaxis of systemic fungal infections or suppression of infection: IV infusion 0.5–1 mg/kg 1–3 times each week. Visceral leishmaniasis: IV infusion 0.5–1 mg/kg on alternate days for 14–20 doses. Amoebic meningitis: IV infusion 1 mg/kg daily. Intrathecal amphotericin may also be required; consult infectious diseases specialist. Amphotericin, cholesteryl sulfate complex (Amphocil®): IV infusion, 3–4 mg/kg once daily; up to 6 mg/kg once daily has been used. Amphotericin, lipid complex (Abelcet®): IV infusion, 5 mg/kg daily. Single dose or short courses (5 days) appear to be effective in visceral leishmaniasis, seek specialist advice. Amphotericin, liposomal (AmBisome®): Treatment may start at 1–3 mg/kg daily, increase stepwise up to 5 mg/kg daily if necessary for severe infection. Lower doses may be effective but clinical trial data are limited. Cumulative dose of 1–3 g over 3–4 weeks has been used for systemic fungal infections. Cumulative dose of 60 g over 9 months has been given without significant toxicity. Prophylaxis in liver transplant patients: IV infusion 1 mg/kg for 5 successive days following transplantation. Systemic fungal infections: IV infusion 3–5 mg/kg once daily as required. Visceral leishmaniasis: IV infusion 1–1.5 mg/kg daily for 21 days; or 3 mg/kg daily for 10 days. Treatment and prophylaxis of oral candidiasis: 1 lozenge (10 mg) 4 times daily (for 1–2 weeks for treatment).

**Administration instructions**

Conventional: Reduce risk of thrombophlebitis by using large peripheral veins or a central venous catheter, using heparin, changing venous access sites frequently, and infusing over longer periods. To minimise infusion-related reactions, infuse the initial dose slowly over 2–6 hours; alternatively, infuse the first 1 mg of the initial dose over 30 minutes, then give the remainder over 2–4 hours. Tolerance to infusion-related reactions increases with each subsequent dose, which may allow infusion rate to be increased from initial rate if required. Do not mix with lipid emulsion; stability, efficacy and toxicity are unclear. Protect IV infusion from light. Cholesteryl sulfate complex: Give a test dose (eg 10 mL of the final preparation) over 15–30 minutes. Give the rest of the infusion at a rate of 1–2 mg/kg/hour. Shorten this to a minimum of 2 hours if there have been no reactions; increase the time if the patient reacts. Lipid complex: Agitate IV infusion bag to ensure adequate mixing before administration. If infusion time exceeds 1 hour, re-agitate. Give a 1 mg test dose over 15 minutes, then give the rest of the infusion at a rate of 2.5 mg/kg/hour. Liposomal: Give IV infusion over 30–60 minutes.

**Patient counselling**

It is best to use the lozenge after (rather than before) a meal or drink. Continue to use them for about 2 days after your symptoms disappear.

**Practice points**

- measure creatinine and blood urea before starting treatment (and then every alternate day while dosage is increasing for conventional amphotericin); monitor creatinine, potassium, magnesium and blood urea at
least 3 times a week and complete blood picture and hepatic function twice a week during treatment and until stable after treatment

- IV amphotericin is the traditional drug of choice for most serious systemic fungal infections; however azole antifungals are frequently suitable as primary treatment for cryptococcal meningitis (fluconazole), IV catheter-associated candidaemia (fluconazole) or invasive aspergillosis (voriconazole); seek specialist advice
- resistance to amphotericin is uncommon (except Scedosporium spp.)
- lipid formulations of amphotericin or caspofungin are alternatives to voriconazole for treating suspected or proven acute aspergillosis
- lipid formulations of amphotericin can be used to treat infections due to Fusarium spp. or Zygomycetes
- conventional amphotericin is as effective as liposomal amphotericin in treating cryptococcal meningitis
- other formulations of amphotericin reduce nephrotoxicity compared to the conventional form, allowing higher doses to be tolerated; the few comparative clinical trials between conventional and other formulations appear to show similar efficacy

Conventional
- can be used with flucytosine for cryptococcal meningitis
- amphotericin is the preferred treatment for life-threatening histoplasmosis in HIV patients
- use an antihistamine, paracetamol and/or hydrocortisone to prevent or treat infusion reactions
- amphotericin may be given by other routes, eg intrathecal injection and bladder instillation, seek specialist advice
- record total amphotericin dose; total IV dose >3–5 g in adults increases the risk of permanent renal damage

Lipid complex
- cumulative dose of 56.6 g has been given without significant toxicity

Liposomal
- an antihistamine can be used to prevent or treat infusion reactions

Products

**AMPHOTERICIN B VIAL 50 MG/VIAL (AMPHOTRECIN B®, FUNGIZONE®)**

**CASPOFUNGIN**

**Mode of action**
Fungicidal echinocandin. Inhibits synthesis of fungal cell wall glucan, altering cell membrane permeability.

**Indications**
- Invasive aspergillosis in patients refractory to, or intolerant of, other antifungal therapy
- Invasive candidiasis, including candidaemia
- Oesophageal candidiasis
- Empirical treatment of febrile neutropenia in patients who are unresponsive to antimicrobials

**Contraindications**
- Allergy to caspofungin
- Breast feeding

**Specific considerations**
- Hepatic impairment: Reduce dose in moderate impairment (Child–Pugh score 7–9); avoid in severe impairment (Child–Pugh score >9).
- Pregnancy: No data; ADEC category B3.
- Breastfeeding: No data available.

**Adverse effects**
- Common: fever, phlebitis at injection site, flushing, chills, nausea, vomiting, diarrhoea, rash, itch, eosinophilia, anaemia, raised ALP, increased urine protein, reduction in plasma potassium, headache
- Rare: hepatic dysfunction, possible histamine-mediated symptoms (including facial swelling, bronchospasm, anaphylaxis)

**Dosage**
- 70 mg initially, followed by 50 mg every 24 hours. Maximum 70 mg daily.
- Oesophageal candidiasis, 50 mg daily.
- Moderate hepatic impairment: 70 mg initially, followed by 35 mg daily.
- Oesophageal candidiasis, 35 mg daily.

**Administration instructions**
Give IV infusion in sodium chloride 0.9% over 60 minutes. Do not use glucose solutions (caspofungin is unstable).

**Practice points**
- mainly active against Aspergillus and all Candida spp.; ineffective against Cryptococcus
- caspofungin or lipid formulations of amphotericin are alternatives to voriconazole for treating suspected or proven acute aspergillosis
- at least as effective as amphotericin for invasive candidiasis and oesophageal candidiasis
- alternative to amphotericin or azole antifungals for candidaemia or invasive candidiasis
- alternative to liposomal amphotericin in empirical treatment of febrile neutropenia unresponsive to antibacterials
- duration of treatment is determined by severity of illness and response to treatment
- there is no benefit in using doses >50 mg daily when treating oesophageal candidiasis
- there are limited data about the use of caspofungin with other antifungals

**Products**

**CASPOFUNGIN VIAL 70 MG (CANCIDAS®)**

**FLUCONAZOLE**

**Mode of action**

Fungistatic. Azoles impair the synthesis of ergosterol in fungal cell membranes leading to their breakdown; cell leakage and death occur by lytic activity of the host defence system.

**Indications**

- Acute or recurrent mucocutaneous candidiasis
- Vulvovaginal candidiasis where topical therapy has failed
- Candidiasis due to susceptible strains of Candida (not C. krusei or C. glabrata)
- Tinea corporis, cruris or pedis resistant to topical therapy
- Onychomycosis (if alternatives have failed or are not tolerated)
- Treatment and prophylaxis of cryptococcal meningitis if amphotericin is not tolerated, or after initial treatment with amphotericin
- Coccioidiomycosis, Cryptococciosis, Histoplasmosis
- Prophylaxis/prevention of relapse of candidal infection in immunocompromised people

**Contraindications**

- Allergic reaction to azole antifungals
- Treatment with cisapride

**Specific considerations**

- Risk factors for prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
- Renal impairment: Reduce dose.
- Pregnancy: Repeated high dose contraindicated, single 150 mg dose appears safe; ADEC category D.
- Breastfeeding: Appears safe to use.

**Adverse effects**

- Common: rash, headache, dizziness (infrequent with ketoconazole), nausea, vomiting, abdominal pain, diarrhoea, elevated liver enzymes
- Infrequent: anorexia, fatigue, constipation
- Rare: thrombocytopenia, other blood dyscrasias, serious hepatotoxicity including hepatic failure, anaphylactic/anaphylactoid reactions, oliguria, hypokalaemia, dizziness, paraesthesia, seizures, alopecia, Stevens–Johnson syndrome; prolonged QT interval, torsades de pointes (both very rare)

**Dosage**

Use the same dose for oral and IV administration.

- Adult: Oropharyngeal/oesophageal candidiasis: 50–200 mg daily (the lower doses are usually used for oral candidiasis).
- Vulvovaginal candidiasis where topical therapy failed: Treatment, 150 mg single dose. Prophylaxis, initially 2–3 doses of 150 mg given 3 days apart, then 100–150 mg once a week for up to 6 months in severe recurrent cases. Severe tinea where topical therapy failed/inappropriate: 150 mg once each week for 4 weeks.
- Onychomycosis: 150–300 mg once each week for 3–12 months.
- Systemic candidiasis: 200–400 mg daily (higher doses may be required in neutropenic patients).
- Treatment of cryptococcal meningitis: 800 mg loading dose, then 400 mg daily.
- Prophylaxis of cryptococcal meningitis: 100–200 mg daily (especially for secondary prophylaxis in HIV unless...
immune restoration present for >6 months).
Prophylaxis of mucocutaneous, systemic and disseminated fungal infections: Bone marrow transplantation, 100–400 mg daily. HIV, 150 mg each week or 50–100 mg daily.
Child
Neonates: Dose as for children but give every 3 days in the first 2 weeks of life; every 2 days in second 2 weeks.
Infants and children: Superficial and oral candidiasis, 6 mg/kg (maximum 200 mg) once daily on day 1, then 3 mg/kg once daily.
Systemic infections, 12 mg/kg (maximum 400 mg) once daily on day 1, then 6 mg/kg once daily, (12 mg/kg once daily if immunocompromised or there is severe infection).
Renal impairment: Mild-to-moderate, usual dose for first 2 days, then give half dose daily.
Severe impairment, seek specialist advice.
Administration instructions
Give IV infusion at 200 mg/hour.
Patient counselling
Tell your doctor if you feel unusually tired, nauseous or are not eating, or if you notice dark urine, pale faeces or yellowing of the whites of your eyes or skin. This medicine interacts with many drugs; tell your doctor and pharmacist that you are taking this medicine before starting or stopping any medicines, including herbal and over-the-counter products.
Practice points
- use topical antifungal preparations first for mucocutaneous and vulvovaginal candidiasis; reserve fluconazole for resistant cases
- excellent oral absorption; use IV only if oral administration is not possible
- less toxic than IV amphotericin
- oral fluconazole may be as effective as, and is better tolerated than, IV amphotericin for invasive candidiasis due to susceptible Candida species; however, IV amphotericin remains the drug of choice for severe candidaemia before testing of Candida isolate
- amphotericin (with or without flucytosine) is still considered the initial drug of choice for cryptococcal meningitis; fluconazole is the drug of choice for maintenance treatment
- the use of fluconazole may result in overgrowth of non-susceptible strains of Candida
- measure liver function and serum potassium concentration at baseline and at regular intervals, depending on dose and duration of treatment

Products
FLUCONAZOLE CAPS 50 MG (CANDIVAST®, DIFLAZOL®, DIFLUCAN®, FLUCAND®, FLUCOHEAL®, FUNGIMID®, FUNZOL®)
FLUCONAZOLE CAPS 150 MG (CANDIVAST®, DIFLAZOL®, DIFLUCAN®, FLUCAND®, FLUCOHEAL®, FLUCOVER®, FLUCOZAL®, FUNGIMID®, FUNZOL®)
FLUCONAZOLE VIAL 2 MG/ML 100 ML VIAL (DIFLUCAN®, FLUCAND®)

ITRACONAZOLE
Mode of action
Same as Fluconazole.
Indications
Marketed: Dermatophyte and superficial Candida infection, pityriasis versicolor and onychomycosis unresponsive to topical treatment (capsules)
Mucocutaneous candidiasis in immunocompromised people (liquid, capsules)
Systemic or disseminated fungal infections due to susceptible fungi, e.g. aspergillosis, blastomycosis, histoplasmosis, Scedosporium species (capsules)
Vulvovaginal candidiasis where topical therapy has failed (capsules)
Prophylaxis of fungal infections in neutropenic patients (liquid)
Accepted: Secondary prophylaxis of systemic fungal infection in HIV patients
Contraindications
Manufacturer contraindicates use with many drugs, and specifically ergot alkaloids, oral midazolam, pimozide, quinidine, simvastatin and triazolam
Allergic reaction to azole antifungals

Treatment with cisapride

**Specific considerations**

Peripheral neuropathy: may worsen with long term itraconazole use; avoid use.

Heart failure: may precipitate or worsen existing heart failure; use only if necessary; use with caution if there are risk factors and high doses of itraconazole are needed.

Negative inotropic drugs, e.g. calcium channel blockers: itraconazole has a negative inotropic action and may add to their effect.

Hepatotoxic drugs—more likely to develop hepatotoxicity with itraconazole.

Cystic fibrosis: may not achieve therapeutic concentrations of itraconazole; consider using alternative antifungal if response is poor.

Immunocompromised: absorption from capsules may be decreased; consider using oral liquid or alternative antifungal if response is poor.

Decreased gastric acidity, eg achlorhydria, treatment with a PPI: impairs absorption from capsule; give with Coke® and monitor clinical response.

Renal impairment: Absorption of itraconazole may be lower in patients with renal impairment; may need to adjust dose.

Hepatic impairment: More likely to develop hepatotoxicity with itraconazole.

Pregnancy: Avoid use; ADEC category B3.

Breastfeeding: avoid use

**Adverse effects**

Common: dyspepsia, anorexia, fatigue, itch, rash, headache, dizziness, nausea, vomiting, abdominal pain, diarrhoea, elevated liver enzymes, constipation

Infrequent: insomnia, somnolence, gynaecomastia, impotence

Rare: hypertension (high dose), peripheral oedema, pulmonary oedema, heart failure, peripheral neuropathy, alopecia, Stevens–Johnson syndrome, hypokalaemia (especially high dose), reversible adrenal insufficiency (high dose) thrombocytopenia, other blood dyscrasias, serious hepatotoxicity including hepatic failure, anaphylactic/anaphylactoid reactions

**Dosage**

Capsules and oral liquid are not interchangeable.

Adult

Oropharyngeal candidiasis

Oral capsules, 100–200 mg daily for 28 days.

Oral liquid, 200 mg daily or 100 mg twice daily for 7 days.

Higher doses and/or longer duration may be required if initial treatment fails. Drug resistance should be considered;

Severe, recurrent vulvovaginal candidiasis: Oral capsules, 200 mg twice daily for 1 day; or 200 mg daily for 3 days;

Systemic or disseminated fungal infections

Oral capsules, 200 mg daily; up to 200 mg twice daily in severe disease. See manufacturer's product information.

Secondary prophylaxis in HIV, oral capsules, 200 mg once daily (or twice daily if there is impaired absorption).

Prophylaxis in neutropenic patients, oral liquid, 2.5 mg/kg twice daily until neutrophil recovery.

Tinea corporis, tinea cruris: Oral capsules, 100 mg daily for 2 weeks.

Tinea pedis, tinea manus: Oral capsules, 100 mg daily for 4 weeks.

Onychomycosis (due to Candida or dermatophytes)

Standard treatment, 200 mg daily for 3 months.

Pulse treatment, 200 mg twice daily for 1 week; use 2 pulse treatments for fingernail infections, 3 for toenail infections. Separate pulse treatments by a 3-week drug-free interval.

Pityriasis versicolor: Oral capsules, 200 mg daily for 1 week.

**Patient counseling**

This medicine interacts with many drugs; tell your doctor and pharmacist that you are taking this medicine before starting or stopping any medicines, including herbal and over-the-counter products.

Capsules, take with food for best absorption. Do not take antacids within 2 hours of itraconazole capsules as they will interfere with its absorption.

Oral liquid, take on an empty stomach, at least 1 hour before food.

Tell your doctor if you feel unusually tired, nauseous or are not eating; or if you notice dark urine, pale faeces or yellowing of the whites of your eyes or skin.

**Practice points**
itraconazole takes 1–2 weeks to reach steady state concentrations
consider drug resistance if treatment of oropharyngeal candidiasis fails; amphotericin may be required in unresponsive cases
effective for mild-to-moderate histoplasmosis and long term suppressive treatment; amphotericin is the preferred treatment for life-threatening histoplasmosis in HIV patients
possible second line treatment for aspergillosis in non-immunosuppressed people
has advantages over griseofulvin and ketoconazole of being well tolerated and more effective, with a broad spectrum of activity for superficial infections
bioavailability of itraconazole from the oral liquid taken in the fasting state is 60% higher than from a capsule taken with a meal
absorption of itraconazole from capsules requires acidic stomach pH (absorption from oral liquid is unaffected by pH)
monitor liver function tests and serum potassium if treatment given for >1 month (if pre-existing risk factors monitor during any length of treatment); stop treatment and test liver function if symptoms of hepatic dysfunction develop

Products
ITROCANAZOLE CAPS 100 MG (CONAZOLE®, SPORAL®, SPORAVAST®)

VORICONAZOLE
Mode of action
Same as Fluconazole.
Indications
Invasive aspergillosis
Serious Candida infections, including C. krusei
Serious infections caused by Scedosporium (S. prolificans less susceptible than S. apiospermum) and Fusarium spp., and other serious fungal infections in patients intolerant of, or refractory to, other treatment

Contraindications
Manufacturer contraindicates treatment with many drugs, including carbamazepine, efavirenz, ergot alkaloids, phenobarbital, pimozide, quinidine, rifampicin, ritonavir and sirolimus
Allergic reaction to azole antifungals

Treatment with cisapride

Specific considerations
Risk factors for prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
Diabetes, hereditary fructose intolerance, sucrase–isomaltase deficiency, glucose-galactose malabsorption: oral liquid contains sucrose 0.54 g/mL.
Renal impairment: If creatinine clearance <50 mL/minute, use oral route; no dose adjustment necessary; avoid IV route as injection solvent accumulates.
Hepatic impairment: Reduce dose in mild-to-moderate hepatic impairment; no adjustment in acute hepatic injury, but monitor liver function closely.
Pregnancy: No data; avoid use; ADEC category B3.
Breastfeeding: Azoles are excreted into breast milk; avoid using voriconazole if possible.

Adverse effects
Visual abnormalities and abnormal liver function tests appear to be dose-related.
Common: rash, headache, dizziness, nausea, vomiting, abdominal pain, diarrhoea, elevated liver enzymes, thrombocytopenia, visual changes, injection site reactions, infusion reactions, hypotension, photosensitivity, cheilitis, thrombocytopenia, anaemia, hypokalaemia, confusion, peripheral oedema, pulmonary oedema, respiratory distress syndrome, itch, fever; altered taste (oral liquid)
Infrequent: constipation, acute renal failure, arrhythmias, urticaria
Rare: blood dyscrasias, serious hepatotoxicity including hepatic failure, anaphylactic/anaphylactoid reactions, renal tubular necrosis, Stevens–Johnson syndrome, toxic epidermal necrolysis, increased QT interval, torsades de pointes, lymphadenopathy

Visual changes
About 30% people in clinical trials had altered/enhanced visual perception, blurred vision, colour changes or photophobia within 30 minutes of dosing. These are dose-related, reversible and apparently (to the patient) resolve within an hour. However, healthy volunteers taking voriconazole for 28 days had retinal abnormalities during this
period which returned to normal 14 days after the end of this time.

**Infusion reactions**
May occur at the start of infusion, and include anaphylactoid reactions, fever, flushing, sweating, dyspnoea, nausea, itch and rash. Consider stopping voriconazole if they are severe.

**Dosage**

**Adult**

**Loading**
- IV, 6 mg/kg every 12 hours for 24 hours.
- Oral, >40 kg, 400 mg every 12 hours for 24 hours.
- Oral, <40 kg, 200 mg every 12 hours for 24 hours.

**Maintenance IV**
- 3–4 mg/kg every 12 hours.
- With phenytoin, 5 mg/kg every 12 hours.
- With rifabutin, 5 mg/kg every 12 hours.

**Maintenance oral**
- >40 kg, 200 mg twice daily. If response inadequate increase to 300 mg twice daily.
- <40 kg, 100 mg twice daily. If response inadequate increase to 150 mg twice daily.
- With phenytoin, >40 kg, 400 mg twice daily; <40 kg, 200 mg twice daily.
- With rifabutin, >40 kg, 350 mg twice daily; <40 kg, 200 mg twice daily.

**Child 2–12 years**
Round oral dose to nearest 50 mg if using tablets.
- Loading, IV/oral, 6 mg/kg every 12 hours for 24 hours.
- Maintenance, IV/oral, 4 mg/kg every 12 hours.

Hepatic impairment: Halve the maintenance dose in mild-to-moderate hepatic cirrhosis.

**Administration instructions**
Dilute to concentration of 0.5–5 mg/mL in glucose 5% or sodium chloride 0.9% and infuse over 1–2 hours at no more than 3 mg/kg/hour.

IV solution is incompatible with sodium bicarbonate and parenteral nutrition; do not infuse with blood products or electrolytes; other incompatibilities unknown.

**Patient counselling**
Your vision may be blurred and you may be unable to tolerate bright light while taking voriconazole. Do not drive (especially at night) or operate machinery if you are affected.
Avoid sun exposure; wear a hat, clothing that covers you as much as possible and use a sunscreen.
Take voriconazole either 1 hour before or 1 hour after food.
This medicine interacts with many drugs; tell your doctor and pharmacist that you are taking this medicine before starting or stopping any medicines, including herbal and over-the-counter products.

**Practice points**
- voriconazole is treatment of choice for suspected or proven acute invasive aspergillosis in immunocompromised people
- monitor renal and hepatic function at baseline and during treatment (more frequently if abnormalities develop); consider stopping voriconazole if serious abnormalities occur
- monitor serum creatinine closely if IV route must be used in patients with creatinine clearance <50 mL/minute (injection solvent accumulates)
- monitor visual function if treatment duration >28 days
- monitor for adverse effects of rifabutin, eg uveitis, neutropenia, during combination treatment
- infection with voriconazole-resistant moulds or yeasts, such as Zygomycetes, may occur during treatment or prophylaxis with voriconazole
- can switch to oral administration when clinically indicated; oral bioavailability is very high
- oral liquid is equivalent to tablets in healthy adults

**Products**
- VORICONAZOLE 200 MG/VIAL (VFEND®)
- VORICONAZOLE TABS 200 MG (VFEND®)

**05.03 ANTIVIRAL DRUGS**
See Table 05–09 Classification of antiviral drugs
05.03.01 Herpes simplex and varicella-zoster

The two most important herpesvirus pathogens that are amenable to chemotherapy are herpes simplex virus and varicella–zoster virus.

**HERPES SIMPLEX INFECTIONS**

Herpes infection of the mouth and lips and in the eye is generally associated with herpes simplex virus serotype 1 (HSV-1); other areas of the skin may also be infected, especially in immunodeficiency. Genital infection is most often associated with HSV-2 and also HSV-1. Treatment of herpes simplex infection should start as early as possible and usually within 5 days of the appearance of the infection. In individuals with good immune function, mild infection of the eye and of the lips (herpes labialis or cold sores, is treated with a topical antiviral drug. Primary herpetic gingivostomatitis is managed by changes to diet and with analgesics. Severe infection, neonatal herpes infection or infection in immunocompromised individuals requires treatment with a systemic antiviral drug. Primary or recurrent genital herpes simplex infection is treated with an antiviral drug given by mouth. Persistence of a lesion or recurrence in an immunocompromised patient may signal the development of resistance. Specialist advice should be sought for systemic treatment of herpes simplex infection in pregnancy.

**VARICELLA–ZOSTER INFECTIONS**

Regardless of immune function and the use of any immunoglobulins, neonates with chickenpox should be treated with a parenteral antiviral to reduce the risk of severe disease. Chickenpox in otherwise healthy children between 1 month and 12 years is usually mild and antiviral treatment is not usually required. Chickenpox is more severe in adolescents and adults than in children; antiviral treatment started within 24 hours of the onset of rash may reduce the duration and severity of symptoms in otherwise healthy adults and adolescents. Antiviral treatment is generally recommended in immunocompromised patients and those at special risk (e.g., because of severe cardiovascular or respiratory disease or chronic skin disorder); an antiviral is given for 10 days with at least 7 days of parenteral treatment. Pregnant women who develop severe chickenpox may be at risk of complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy. In herpes zoster (shingles) systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7–10 days. Immunocompromised patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug. Chronic pain which persists after the rash has healed (postherpetic neuralgia) requires specific management. Those who have been exposed to chickenpox and are at special risk of complications may require prophylaxis with varicella-zoster immunoglobulin.

**Choice**

Aciclovir is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella–zoster and the systemic and topical treatment of herpes simplex infections of the skin and mucous membranes. It is used by mouth for severe herpetic stomatitis. Aciclovir eye ointment is used for herpes simplex infections of the eye; it is combined with systemic treatment for ophthalmic zoster.

Valaciclovir is an ester of aciclovir, licensed for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); it is also licensed for preventing cytomegalovirus disease following renal transplantation. Famiclovir or valaciclovir are suitable alternatives to aciclovir for oral lesions associated with herpes zoster. Valaciclovir once daily may reduce the risk of transmitting genital herpes to heterosexual partners—specialist advice should be sought. Ganciclovir is related to aciclovir but it is more active against cytomegalovirus; it is also much more toxic than aciclovir and should therefore be prescribed only when the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the initial treatment of CMV retinitis. Ganciclovir causes profound myelosuppression when given with zidovudine; the two should not normally be given together particularly during initial ganciclovir therapy. The likelihood of ganciclovir resistance increases in patients with a high viral load or in those who receive the drug over a long duration; cross-resistance to cidofovir is common. Valaciclovir is licensed for prevention of cytomegalovirus disease following renal transplantation.
**VIRAL HEPATITIS**

Treatment for viral hepatitis should be initiated by a specialist. The management of uncomplicated acute viral hepatitis is largely symptomatic. Early treatment of acute hepatitis C with interferon alfa [unlicensed indication] may reduce the risk of chronic infection. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. For details on immunisation against hepatitis A and B infections, (active immunisation) and (passive immunisation).

**Chronic Hepatitis B**

Interferon alfa is used in the treatment of chronic hepatitis B but its use is limited by a response rate of less than 50%, and relapse is frequent. If no improvement occurs after 3–4 months of treatment, interferon alfa should be discontinued. Interferon alfa is contra-indicated in patients receiving immunosuppressant treatment (or who have received it recently). The manufacturers of interferon alfa contra-indicate its use in decompensated liver disease but low doses can be used with great caution in these patients. Peginterferon alfa-2a is also licensed for the treatment of chronic hepatitis B and may be preferable to interferon alfa.

Lamivudine is used for the initial treatment of chronic hepatitis B. It can also be used in patients with decompensated liver disease. Treatment should be continued if there is no loss of efficacy and until seroconversion is adequate (consult product literature); it is continued long-term in decompensated liver disease. Hepatitis B viruses with reduced susceptibility to lamivudine have emerged following extended therapy. In patients infected with HIV and hepatitis B, lamivudine should be given only as part of combination antiretroviral therapy and in a dose appropriate for treating HIV; the use of lamivudine alone is likely to result in lamivudine-resistant HIV.

**Chronic Hepatitis C**

Before starting treatment, the genotype of the infecting hepatitis C virus should be determined and the viral load measured as this may affect choice of treatment regimen. A combination of ribavirin (see Respiratory Syncytial Virus) and peginterferon alfa is used for the treatment of chronic hepatitis C (see NICE guidance, below). The combination of ribavirin and interferon alfa is less effective than the combination of peginterferon alfa and ribavirin. Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Ribavirin monotherapy is ineffective.

**NICE guidance (peginterferon alfa, interferon alfa, and ribavirin for chronic hepatitis C).**

NICE has recommended (January 2004) that the combination of peginterferon alfa and ribavirin should be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years:

- not previously treated with interferon alfa or peginterferon alfa;
- treated previously with interferon alfa alone or in combination with ribavirin;
- whose condition did not respond to peginterferon alfa alone or responded but subsequently relapsed.

Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Interferon alfa for either monotherapy or combined therapy should be used only if neutropenia and thrombocytopenia are a particular risk. Patients receiving interferon alfa may be switched to peginterferon alfa.

The duration of treatment depends on genotype and viral load (full guidance available at www.nice.org.uk/TA075).

**ACICLOVIR**

**Mode of action**

Following phosphorylation first by cellular then by viral enzymes, guanine analogues inhibit viral DNA polymerase and consequently DNA synthesis.

**Indications**

Primary and recurrent genital herpes simplex
Prevention of recurrent genital herpes simplex
Herpes simplex encephalitis
Acute chickenpox (varicella zoster) in immunocompromised patients
Shingles (varicella zoster virus reactivation)
Acute mucocutaneous herpes simplex virus infections in immunocompromised patients
Herpetic eye infections, see ACICLOVIR (eye)
Labial herpes simplex (cold sores), see ACICLOVIR (skin)

**Contraindications**

Previous serious adverse reactions to individual drug or metabolite

**Specific considerations**

Neurological abnormalities: increased risk of reversible encephalopathic changes, e.g. seizures, hallucinations with IV aciclovir.

Dehydration: aciclovir crystals may precipitate in renal tubules and impair renal function.

Renal impairment: Increases risk of nephrotoxicity and neurological adverse effects; dose adjustment required.
Pregnancy: Safe to use (extensive clinical experience); ADEC category B3.
Lactation: Safe to use.

**Adverse effects**

Common: nausea, vomiting, diarrhoea, hallucination (high dose), headache, encephalopathy (has been reported in 1% patients with IV use), injection site reactions
Infrequent: agitation, vertigo, confusion, dizziness, oedema, renal impairment, arthralgia, sore throat, constipation, abdominal pain, rash, weakness
Rare: coma, convulsions, neutropenia, leucopenia, crystalluria, anorexia, fatigue, hepatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis, anaphylaxis

**Dosage**

**Adult**
Primary genital herpes simplex, oral, 400 mg 3 times daily for 5–10 days.
Recurrent genital herpes simplex, oral, 400 mg 3 times daily or 800 mg twice daily for 3–5 days.
Prevention of recurrent genital herpes simplex, oral, 200 mg 2–3 times daily for up to 6 months (longer duration may be needed in some people).
Shingles, oral, 800 mg 5 times daily for 7 days.
Disseminated shingles, IV, 5–10 mg/kg every 8 hours.
Chickenpox or shingles in immunocompromised patients, herpes simplex encephalitis, IV, 10 mg/kg every 8 hours.

**Child**

<3 months
Herpes simplex, preterm, IV, 20 mg/kg every 12–24 hours or less frequently depending on gestational age; term, IV, 20 mg/kg every 8 hours.
3 months – 12 years
Herpes simplex (non-encephalitis) or chickenpox with complications, IV, 250 mg/m2 every 8 hours.
Herpes simplex encephalitis, shingles (eye involvement), chickenpox encephalitis, IV, 500 mg/m2 every 8 hours.
Herpes simplex (non-encephalitis), oral, <2 years of age, 100 mg 5 times a day; 2 years and over, 200 mg 5 times a day.
3 months – 12 years (immunocompromised)
Chickenpox and shingles (including eye involvement), herpes simplex (encephalitis and non-encephalitis), IV, 500 mg/m2 every 8 hours.
Treatment of herpes simplex (non-encephalitis), oral, <2 years, 200 mg 5 times a day; 2 years and over, 400 mg 5 times a day.
Prophylaxis of herpes simplex (non-encephalitis), oral, <2 years, 100 mg 3–4 times a day; 2 years and over, 200 mg 3–4 times a day.

Renal impairment
Primary and recurrent genital herpes simplex, oral, mild-to-moderate impairment, 200 mg every 8 hours; severe impairment, 200 mg every 12 hours.
Shingles, oral, moderate impairment, 800 mg every 8 hours; severe impairment, 800 mg every 12 hours.
IV aciclovir, adjust dose according to degree of impairment:
mild, 5–10 mg/kg every 12 hours
moderate, 5–10 mg/kg every 24 hours
Severe, 2.5–5 mg/kg every 24 hours and after haemodialysis.

**Patient counselling**

Take every 4 hours during waking hours if taking 5 times daily.
Make sure that you drink plenty of fluids (at least 1.5–2 L daily).
If you wish, you can disperse tablets in water.
This medication may make you feel dizzy or confused. Don't drive or operate machinery if you are affected.

**Practice points**

- ensure adequate hydration of people receiving IV treatment (especially high doses) to minimise renal adverse effects; changes in renal function during treatment usually respond to rehydration, dosage reduction or stopping the drug
- avoid extravasation as injection is alkaline (pH 11)
- chickenpox in a pregnant woman may be associated with severe morbidity and mortality; consider treatment (especially in the third trimester); consult an infectious diseases physician for management
- cross-resistance may occur between agents due to their similar mechanisms of action and activation pathways
Shingles

- start treatment as soon as possible; for best response start within 48 hours of onset of rash; little benefit if treatment is delayed beyond 72 hours unless patient is immunocompromised or has progressive clinical state
- aciclovir seems less effective than famciclovir and valaciclovir in reducing duration of post-herpetic neuralgia

Products

ACICLOVIR TABS 800 MG (NOVIRAL®, SUPRAVIRAN®, VIRPES®, ZOVIRAX®)

ACICLOVIR TABS/CAPS 200 MG (CYCLOHERP®, DUVIMEX®, HERPAVIR®, SUPRAVIRAN®, VIRPES®, VIRUSTAT®)

ACICLOVIR VIAL 250 MG/VIAL (MEDOVIR®, SUPRAVIRAN®, ZOVIRAX®)

VALACICLOVIR

Valciclovir is a pro-drug of aciclovir.

Mode of action

Same as Aciclovir.

Indications

Primary and recurrent genital herpes simplex
Prevention of recurrent genital herpes simplex
Reduction of genital herpes simplex transmission from people who have recurrent infection (<10 episodes/year) and a partner without serological evidence of infection
Shingles (varicella zoster virus reactivation), including ophthalmic disease
Prevention of CMV disease following organ transplantation

Contraindications

Serious adverse reactions to individual drug or metabolite

Specific considerations.

Renal impairment: Increased risk of neurological adverse effects; dose adjustment is required.

Pregnancy: Metabolised rapidly to aciclovir; no evidence of adverse effects; less clinical experience than with aciclovir; ADEC category B3.

Breastfeeding: Limited data available for valaciclovir; however, aciclovir is safe to use.

Adverse effects

As aciclovir is the active metabolite of valaciclovir, any adverse effect found with aciclovir can be expected. Neurological effects are more likely to occur in people with renal impairment or those taking high doses for CMV prophylaxis.

Infrequent: agitation, vertigo, renal impairment

Rare: leucopenia, thrombocytopenia, coma, tremor, ataxia, encephalopathy, psychotic symptoms

Dosage

Adult

Primary genital herpes simplex: 500 mg twice daily for 5–10 days.
Recurrent genital herpes simplex: 500 mg twice daily for 3 days.

Prevention of genital herpes simplex: Immunocompetent; 500 mg once daily; 1 g once daily in patients with 10 or more recurrences each year who break through with lower dose. Use for up to 6 months (longer duration may be needed in some people). Immunocompromised; 500 mg twice daily

Prevention of genital herpes simplex transmission: 500 mg once daily.

Shingles: 1 g 3 times daily for 7 days.
Prevention of CMV disease: 2 g 4 times daily for 90 days.

Renal impairment:

Shingles:
moderate impairment, 1 g twice daily
Severe impairment, 1 g daily.

Genital herpes simplex in severe impairment:
treatment, 500 mg daily
prevention (immunocompetent), 250 mg daily
Prevention (immunocompromised), 500 mg daily.
Prevention of CMV disease, see manufacturer's product information.
Child: 20 mg/kg 3 times a day.

**Patient counselling**
Drink plenty of fluids (at least 1.5 L daily).
Reduction of transmission of genital herpes: taking valaciclovir will help reduce your risk of giving genital herpes to your partner; using condoms as well will also help.
This medication may make you feel dizzy or confused. Don't drive or operate machinery if you are affected.

**Practice points**
- valaciclovir is a pro-drug of aciclovir
- for shingles, start treatment as soon as possible; best response when started within 48 hours of onset of rash; little benefit if treatment is delayed beyond 72 hours unless patient has progressive clinical state or is immunocompromised
- taking valaciclovir reduces transmission of genital herpes simplex slightly; 59 people need to take it for 8 months to prevent 1 infection
- cross-resistance may occur between agents due to their similar mechanisms of action and activation pathways

**Products**
VALACICLOVIR TABS 500 MG (AS HCL) (VALTREX®)

05.03.02 Other antiviral drugs

**GANCICLOVIR**

**Mode of action**
Same as Aciclovir.

**Indications**
Marketed: Sight-threatening CMV retinitis in severely immunocompromised people
CMV pneumonitis in bone marrow transplant recipients
Prevention of CMV disease in bone marrow and solid organ transplant recipients
Confirmed CMV retinitis in people with AIDS (intravitreal implant, seek specialist advice)
Accepted: Acute CMV colitis in HIV/AIDS
CMV pneumonitis in immunosuppressed patients

**Contraindications**
Pregnancy, Breastfeeding
Serious adverse reactions to individual drug or metabolite

**Specific considerations**
Neutropenia: avoid use, particularly if neutrophil count is <0.5x10^9 cells/L.
Thrombocytopenia: avoid use, particularly if platelet count is <25x10^9 cells/L.
Anaemia: avoid use, particularly if haemoglobin is <80 g/L.
Bone marrow suppression: may be more susceptible to myelosuppressive effects of ganciclovir; dosage adjustment and/or blood examination each week (or more frequently) may be required.
Treatment with imipenem: may increase risk of seizures; avoid combination.
Treatment with zidovudine: some clinicians recommend stopping zidovudine or changing to alternative antiretroviral agent during ganciclovir induction treatment because of the added risk of neutropenia.
Renal impairment: Dosage adjustment required for moderate and severe impairment.
Children: Avoid use if possible; limited data on safety and efficacy; potential long term carcinogenic effects and long term adverse effects on reproductive function; seek specialist advice. Not indicated for the treatment of congenital or neonatal CMV infection.

**Adverse effects**
Common: granulocytopenia, neutropenia, anaemia, thrombocytopenia, fever, nausea, vomiting, dyspepsia, diarrhoea, abdominal pain, flatulence, anorexia, raised liver enzymes, headache, confusion, hallucination, seizures, pain and phlebitis at injection site (due to high pH), sweating, rash, itch, increased serum creatinine and blood urea
concentrations
Infrequent: chest pain, chills, mouth ulceration, cough, dry mouth, drowsiness

**Dosage**

CMV retinitis
Induction, IV, 5 mg/kg every 12 hours for 14–21 days.
Maintenance, IV, 6 mg/kg once daily for 5 days each week; or 10 mg/kg once daily 3 times each week; or 5 mg/kg once daily every day.
Maintenance, oral, 1 g 3 times daily.
Prevention of CMV disease in transplant recipients
Induction, IV, 5 mg/kg every 12 hours for 7–14 days.
Maintenance, IV, 5 mg/kg once daily every day or 6 mg/kg daily for 5 days each week for up to 100–120 days after transplant.
Maintenance, oral, 1 g 3 times daily for up to 100 days after transplant.
CMV pneumonitis: IV, 5 mg/kg every 12 hours for 14–21 days.
CMV colitis in HIV/AIDS: IV, 5 mg/kg every 12 hours for 14 days.
Renal impairment: Adjust dose according to creatinine clearance. See manufacturer's product information.

**Administration instructions**

Do not give by IM or SC injection.
Ganciclovir is considered to be carcinogenic; handle using cytotoxic precautions.
Infuse IV over 1 hour (usual volume 100 mL).

**Patient counselling**

Swallow the capsules whole. Take them with food as they are absorbed better.
This medication may make you feel dizzy or confused. Don't drive or operate machinery if you are affected.

**Practice points**

- ganciclovir has poor oral bioavailability (approximately 6–9% with food)
- oral ganciclovir is not indicated for induction therapy
- continue induction treatment for 2–3 weeks depending on response; clinical response (generally occurs within 2–3 weeks), monitoring of viral response may be indicated
- if disease progression occurs during maintenance treatment a repeat induction course may be given
- neutropenia is dose-dependent and reversible; usually occurs during the first 1–2 weeks of treatment; try to maintain neutrophil count >0.5x10⁹ cells/L during treatment
- neutropenia is dose-dependent and reversible; usually occurs during the first 1–2 weeks of treatment; try to maintain neutrophil count >0.5x10⁹ cells/L during treatment
- temporarily interrupt treatment if severe neutropenia or thrombocytopenia occur; consider reducing the dose if anaemia or leucopenia occur; neutrophil counts return to baseline 2–5 days after stopping
- adverse renal effects generally occur in the first few weeks of treatment; dose adjustment may be required; toxicity is usually reversible
- intraocular use offers protection only to the eye under treatment; it does not prevent CMV in the untreated eye or protect against extraocular disease; oral ganciclovir often given in addition
- cross-resistance may occur between agents due to their similar mechanisms of action and activation pathways

**Patient monitoring**

- measure complete blood count 2–3 times each week at induction, then each week during maintenance treatment
- monitor electrolytes and renal function 2–3 times each week
- measure liver enzymes before starting treatment, then each month

**Products**

**GANCICLOVIR VIAL 500 MG/VIAL (CYMEVENE®)**

**LAMIVUDINE**

Also known as 3TC.

**Mode of action**

NRTIs are converted by cellular enzymes to active phosphorylated metabolites that inhibit viral reverse transcriptase and viral DNA synthesis, preventing HIV replication.

**Indications**
HIV infection in adults and children, with other antiretrovirals

Chronic hepatitis B with evidence of hepatitis B virus (HBV) replication (children need additional evidence of active hepatic inflammation)

Combination with zidovudine: HIV infection in people >12 years with other antiretrovirals (see Zidovudine)

Combination with abacavir and zidovudine: HIV infection in people >12 years (see Zidovudine)

Contraindications

Serious adverse reactions to individual agent

Specific considerations

Hepatitis B: risk of rebound hepatitis after stopping treatment (may cause severe decompensation in advanced liver disease or transplant recipients).

Treatment with zidovudine: profound anaemia occasionally occurs at start of combination treatment with zidovudine in advanced disease; monitor complete blood count at baseline and then every month for 3 months.

Treatment with zalcitabine: avoid combination with lamivudine.

Weight <40 kg fixed dose combination with abacavir and zidovudine unsuitable; use each drug separately.

Pancreatitis: didanosine, stavudine and lamivudine have been associated with pancreatitis (infrequent in adults but common in children with lamivudine) and may worsen existing pancreatitis; monitor for symptoms and rising amylase or lipase concentrations.

Peripheral neuropathy: didanosine, zalcitabine and stavudine cause peripheral neuropathy and may worsen existing conditions.

Haematological abnormalities: zidovudine and, rarely, lamivudine are myelosuppressive and may exacerbate pre-existing disease.

Risk factors for liver disease: may increase risk of lactic acidosis with hepatomegaly and steatosis.

Renal impairment

Dose reduction required if creatinine clearance <50 mL/minute; do not use fixed dose combinations (give each drug separately).

Hepatic impairment: Severe impairment may increase the risk of adverse effects.

Children: Seek specialist advice.


Avoid combining didanosine and stavudine during pregnancy as fatal lactic acidosis has occurred.

Zidovudine can be used to help prevent vertical transmission in women who would not otherwise require antiretroviral treatment; however, in Australia most women are given combination antiretroviral treatment; seek specialist advice.

Breastfeeding: Breastfed infants of HIV infected mothers are at risk of postnatal transmission. Discourage breastfeeding.

Adverse effects

Common: headache, nausea, vomiting, anorexia, myalgia, peripheral lipoatrophy (especially with long term treatment, more common with stavudine), asymptomatic hyperlactataemia, diarrhoea, abdominal pain, rash, malaise, fatigue, fever, raised liver enzymes, anaemia, neutropenia, thrombocytopenia

Infrequent: pancreatitis, elevated liver enzymes, hepatitis, pancytopenia, leucopenia, myopathy, peripheral neuropathy, pancreatitis (particularly in children)

Rare: symptomatic hyperlactataemia, lactic acidosis (may be more common with stavudine), lactic acidosis with severe hepatomegaly and steatosis (more common in women), pure red cell aplasia

Dosage

HIV

Adult, child >12 years
Tablet, 150 mg twice daily or 300 mg once daily.
Oral liquid, 150 mg (15 mL) twice daily.
Child 3 months – 12 years
Tablet or oral liquid, 4 mg/kg twice daily, up to a maximum of 300 mg daily.

Chronic hepatitis B

Adult, child >12 years: 100 mg once daily.
Child 2–11 years: 3 mg/kg once daily (maximum 100 mg daily).
Coinfection of HIV and hepatitis B: 150 mg twice daily.

Renal impairment: See manufacturer's product information.

Patient counselling

Sometimes this medicine can cause lactic acid to build up in your body and cause symptoms. Tell your doctor
immediately if you have nausea, vomiting, stomach pain, fatigue or weakness..

**Practice points**

- lamivudine is generally well tolerated
- 3TC® oral liquid contains 20% sucrose (1 g/5 mL)
- all NRTIs inhibit reverse transcriptase (after metabolic activation) but the specific site of action differs for each drug; these differences are exploited in combination regimens
- a 3 NRTI regimen is less effective than NNRTI- or PI-based regimens; a regimen such as abacavir, lamivudine and zidovudine (Trizivir®) may be useful where other regimens cannot be used; avoid the combinations of lamivudine and tenofovir with either abacavir or didanosine
- avoid combining:
  - zalcitabine with didanosine, stavudine or lamivudine
  - stavudine with didanosine or zidovudine
  - lamivudine with emtricitabine
  - didanosine with tenofovir
- measure lactate concentration if there is unexplained nausea, anorexia or vomiting, raised liver function tests or hepatomegaly
- stop treatment immediately if lactic acidosis develops or if hyperlactataemia is accompanied by nausea, fatigue, fever, weight loss, abdominal pain, breathlessness, ascending neuromuscular weakness, hepatomegaly or elevated liver enzymes

**HIV**

- if considering restarting fixed dose combination with abacavir check that the patient had no hypersensitivity symptoms during previous use (life-threatening reactions have occurred after restarting abacavir in people who had only 1 symptom of hypersensitivity)
- consider a triple NRTI regimen such as fixed dose combination with abacavir as sole treatment only in those who have potential drug interactions or compliance difficulties

**Hepatitis B**

- test for HBeAg (hepatitis B e antigen) and anti-HBe (hepatitis B e antibody) at the end of 1 year of treatment and then every 3–6 months
- optimal duration of treatment for hepatitis B is unknown, but may be stopped after 1 year of treatment if HBeAg seroconversion occurs (ie development of anti-HBe)
- treat for a further 3–6 months after HBeAg seroconversion to reduce possibility of relapse
- monitor liver function tests for at least 4 months after stopping lamivudine in patients with chronic hepatitis B
- some evidence shows lamivudine delays disease progression in people with advanced fibrosis or cirrhosis

**Products**

**LAMIVUDINE TABS 100 MG (ZEFFIX®)**

**PEGINTERFERON ALFA**

**Indications**
Marketed: Chronic hepatitis B
Accepted: Acute hepatitis C, seek specialist advice
Peginterferon alfa
Chronic hepatitis C in interferon-naive people >18 years with compensated disease, (usually with ribavirin), see Ribavirin with peginterferon alfa
Contraindications
HIV infection with cirrhosis and Child–Pugh score of 6

**Specific considerations**
HIV infection: hepatic decompensation and death may be more likely in people with advanced cirrhosis who are also taking combination antiretroviral treatment.

**Dosage**
Chronic hepatitis B
Interferon alfa-2a
SC/IM, 4.5x10^6 units 3 times a week. If this is tolerated and there is no response after 1 month gradually increase the dose to a maximum of 18x10^6 units 3 times a week. Maintain minimum dose required for response for 4–6 months unless intolerance develops.
Interferon alfa-2b
SC, 3x10^6 units 3 times a week, increasing to 5–10x10^6 units 3 times a week after 1 month if the lower dose is tolerated and there is no response. Maintain minimum dose required for response for 4–6 months unless intolerance develops.

Peginterferon alfa-2a
SC, 180 micrograms once a week for 48 weeks.

Chronic hepatitis C
Use with ribavirin (unless contraindicated) as this is more effective.

For doses with combination products, see Ribavirin with peginterferon alfa.

Interferon alfa-2a and alfa-2b
SC, 3x10^6 units 3 times a week for 12 weeks. Test for hepatitis C RNA and if patient has responded then continue for a total of 6–12 months.

Peginterferon alfa-2a
SC, 180 micrograms once a week.

Peginterferon alfa-2b
SC, 0.5 micrograms/kg (1 microgram/kg may be used for genotype 1) once a week; dose of 1.5 micrograms/kg has been used in trials.

Dose modification
For dose modifications (including guidance about stopping treatment) because of adverse effects during treatment (eg changes in haemoglobin, neutrophil or platelet count), see manufacturer's product information.

Patient counselling
Make sure you know how to give the injections and safely dispose of the needles.
Tell your doctor immediately if you get any jaundice (yellowing of skin and whites of eyes) or easy bruising, or are feeling more depressed or sad than usual.
This medication may make you feel tired, sleepy or confused—avoid driving or using machinery if you feel like this.
Warm by holding in your hand for a few minutes or leave at room temperature for 30 minutes before injecting.

Practice points
- interferon alfa alone is no longer recommended to treat hepatitis C; only use peginterferon alfa alone if the person cannot take ribavirin
- peginterferon alfa-2a and peginterferon alfa-2b are considered clinically equivalent
- when using peginterferon alfa alone test for hepatitis C RNA (HCV RNA) at 12 weeks; if response shown, continue treatment for 48 weeks; if no response (positive for HCV RNA) stop treatment
- test for HCV RNA 6 months after stopping treatment to check response
- increased ALT can occur during treatment for hepatitis B or C; stop treatment if this progresses despite dosage reduction, or if bilirubin increases
- there is increasing evidence that treatment improves liver-related morbidity and mortality

Products
PEGINTERFERON ALFA-2A 135 MCG (PEGASYS®)
PEGINTERFERON ALFA-2A 180 MCG (PEGASYS®)
PEGINTERFERON ALFA-2B 100 MCG (PEG-INTRON®)
PEGINTERFERON ALFA-2B 150 MCG (PEG-INTRON®)

RIBAVIRIN (INHALED)

Mode of action
Nucleoside analogue that interferes with RNA and DNA synthesis, thereby inhibiting protein synthesis and viral replication.

Indications
Serious lower respiratory tract infection with respiratory syncytial virus (RSV) in hospitalised children <2 years of age

Specific considerations
Asthma: deterioration in lung function may occur with inhaled ribavirin; monitor carefully and stop treatment if deterioration occurs.

Adverse effects
Common: worsening lung function, apnoea, pneumothorax, hypotension, anaemia, rash, conjunctivitis

Dosage
Inhale for 12–18 hours/day for 3–7 days, using a solution of 20 mg/mL.
Administration instructions
Develop procedures to minimise environmental exposure to aerosolised ribavirin; knowledge of the correct procedure for use of the nebuliser is essential.
Reconstitute powder and dilute further with water for injection to final volume of 300 mL (final concentration is 20 mg/mL). See manufacturer's product information for administration procedure.

Practice points
- conclusive evidence for benefit of inhaled ribavirin in treating bronchiolitis is lacking
- begin treatment within first 3 days of infection
- do not use for children receiving assisted ventilation as ribavirin may precipitate in the equipment and jeopardise ventilation and gas exchange

Health care workers
- people giving ribavirin inhalation can develop irritated eyes, nose and throat, and rash
- ribavirin can precipitate on contact lenses and cause conjunctivitis, avoid wearing lenses
- the risk to health care personnel (especially if pregnant or breastfeeding) from inhaling ribavirin is uncertain—note, oral ribavirin is contraindicated in pregnancy and breastfeeding should be avoided while it is being taken

Products
RIBAVIRIN CAPS 200 MG (COPEGUS®, REBETOL®, RIBAVIN®)

05.04 ANTIPROTOZOAL DRUGS

05.04.01 Antimalarials

CHLOROQUINE

Mode of action
Rapidly acting schizonticide with some gametocytocidal activity.
May inhibit plasmodial haem polymerase causing accumulation of haem, which is toxic to parasite membranes; interferes with DNA or RNA synthesis; binds to haemoglobin protease; increases intravacuolar pH.

Indications
Marketed: Prophylaxis and treatment of malaria in susceptible organisms (widespread resistance to chloroquine has developed in P. falciparum)
Rheumatoid arthritis (mild)
Systemic lupus erythematosus

Contraindications
Retinal damage, Chloroquine resistance

Specific considerations
Haematological disorders: chloroquine may be myelosuppressive.
G6PD deficiency: observe for haemolytic anaemia.
Myasthenia gravis: symptoms may be exacerbated.
Porphyria: may be exacerbated.
Psoriasis: may be exacerbated.
Epilepsy: avoid use for prophylaxis of malaria as tonic-clonic seizures have been reported.
Treatment with mefloquine—increases risk of cardiotoxicity and convulsions.
Risk factors for prolonging the QT interval, see Prolonged QT interval—may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
Pregnancy: For prophylaxis against malaria, safe to use; ADEC category A.
For treatment of malaria, contact specialised information service; risk/benefit ratio is in favour of use; ADEC category D.
Breastfeeding: Safe to use for malaria prophylaxis.
For other indications, contact specialised information service

Adverse effects
Less common in treatment and prophylaxis of malaria than when used in higher doses for rheumatoid arthritis.
Common: headache, skin eruptions, itch, GI disturbances
Infrequent: psychotic episodes, anxiety, personality changes, visual disturbances (large doses), reversible corneal opacities, irreversible retinopathy (occurs with cumulative doses >100 g)
Rare: hair loss, bleaching of hair, blue–black pigmentation of mucous membranes and skin, photosensitivity, tinnitus,
hearing loss, blood dyscrasias, reversible myopathy, elevation of thyroid stimulating hormone, seizures, arrhythmias, prolonged QT interval (high doses)

**Dosage**

Doses given are in mg of chloroquine base.

**Prophylaxis of chloroquine-sensitive malaria**

Start 1 week before entering, and continue for 4 weeks after leaving, an endemic area.

Chloroquine has been used for prolonged periods (>5 years for prophylaxis).

- **Adult, child >8 years**, 2 tablets (310 mg) once a week.
- **Child 4–8 years**, 1 tablet (155 mg) once a week.
- **Child 1–4 years**, half a tablet (77.5 mg) once a week.

**Treatment of chloroquine-sensitive malaria**

- **Adult**, 4 tablets (620 mg), followed by 2 tablets (310 mg) 6 hours later, then 2 tablets (310 mg) on days 2 and 3 (total dose of 25 mg/kg bodyweight). To eliminate liver forms of *P. vivax* and *P. ovale*, follow with primaquine.
- **Child**, 10 mg/kg, then 5 mg/kg after 6 hours, followed by 5 mg/kg on days 2 and 3.

Dose Equivalence: Chloroquine phosphate 250 mg is equivalent to 155 mg chloroquine base.

**Patient counselling**

Avoid mosquito bites by using repellents and wearing protective clothing. Take chloroquine regularly, at the same time and on the same day each week. Start taking chloroquine 1 week before entering, and continue for 4 weeks after leaving, an endemic area. See a doctor if fever develops within 12 months of possible exposure.

**Practice points**

- before starting use for malaria prophylaxis, ask about visual impairment and record near visual acuity; assess visual acuity once a year and recommend ophthalmological review after 5 years continuous use
- give an additional dose of antimalarial if an oral dose is vomited within 1 hour of administration (or switch to parenteral treatment if necessary)

**Products**

**CHLOROQUINE TABS 150 MG (AS PHOSPHATE) (CHLOROQUINE®)**

**MEFLOQUINE**

**Mode of action**

Mefloquine may form toxic complexes with free haem that damage membranes and interact with other plasmodial components.

**Indications**

Malaria prophylaxis in areas resistant to chloroquine

- Treatment of known or suspected *P. falciparum* malaria as an alternative to quinine
- Treatment of chloroquine-resistant *P. vivax* malaria (seek specialist advice)

**Contraindications**

- Previous or current psychiatric disorders, including depression (if used for prophylaxis)
- Serious adverse effects with quinine or mefloquine
- Epilepsy

**Specific considerations**

- Cardiac disease: may increase risk of arrhythmias.
- Risk factors for prolonged QT interval: may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
- Treatment with quinine, quinidine or chloroquine: additive effects, increasing risk of cardiotoxicity and seizures.
- Hepatic impairment: Avoid use for prophylaxis in severe impairment.
- Surgery: There have been reports of delirium occurring after general anaesthesia.
- Children: Not recommended for use in neonates.
- Pregnancy: Do not use for prophylaxis in the first trimester if possible; an increased number of stillbirths has occurred during pregnancy; ADEC category B3.
- Women should avoid becoming pregnant for 3 months after taking mefloquine.
- Breastfeeding: Safe to use for short term treatment; long term effects have not been studied.

**Adverse effects**

- More frequent with doses used for treatment than for prophylaxis and may occur (or persist) up to several weeks after the last dose.
- Common: nausea, vomiting, diarrhoea, abdominal pain, headache, dizziness, difficulty in performing skilled tasks, sleep disorders (insomnia, abnormal dreams)
Infrequent: rash, myalgia, dyspnoea, visual disturbances, elevated liver enzyme concentrations, chest pain, tachycardia, asymptomatic bradycardia, panic attacks, agitation, aggression, serious neuropsychiatric effects (eg delirium, stupor) can be severe and prolonged
Rare: hyperpyrexia, blood dyscrasias, erythema multiforme, atrioventricular block, prolonged QT interval

Dosage

Doses are expressed in terms of mefloquine base.

Prophylaxis of malaria

Start taking preferably 2–3 weeks before entering, and continue for 2–4 weeks after leaving, an endemic area. Mefloquine prophylaxis may be taken for up to 1 year.

Adult, 250 mg once a week. If it is impossible to take mefloquine for 2–3 weeks before entering the endemic area take 250 mg daily for 3 days, and then once each week.

Child >3 months, 5 mg/kg (maximum 250 mg) once a week. Round dose to nearest quarter tablet.

Treatment of uncomplicated P. falciparum malaria

Adult, 750 mg, followed by 500 mg after 6–8 hours. Where malaria has been acquired in areas of multi-drug resistance use 25 mg/kg (maximum 1.5 g) in 2–3 divided doses.

Child >3 months, 15 mg/kg (maximum 750 mg), followed by 10 mg/kg (maximum 500 mg) after 6–8 hours. Round dose to nearest quarter tablet.

Dose equivalence: 250 mg mefloquine base is equivalent to 274 mg mefloquine hydrochloride.

Patient counselling

Avoid mosquito bites by using repellents and wearing protective clothing. Take mefloquine regularly, at the same time and on the same day each week. It's best to start mefloquine 2–3 weeks before entering, and continue for 2–4 weeks after leaving, an endemic area. See a doctor if a fever develops within 12 months of possible exposure.

Mefloquine may cause dizziness and affect your ability to drive or perform skilled tasks. These effects may continue for up to 3 weeks after the last dose.

People taking mefloquine can feel anxious, depressed, restless or confused, and sometimes these feelings are intense. If you feel affected like this tell your doctor as you may need to stop taking mefloquine.

Practice points

• because of adverse neuropsychiatric reactions, mefloquine should be used as prophylaxis only in areas of chloroquine resistance and when doxycycline is not appropriate
• if psychiatric symptoms, eg depression, occur during prophylactic use, stop treatment with mefloquine and use an alternative antimalarial
• give an additional dose of antimalarial if an oral dose is vomited within 1 hour of administration (or switch to parenteral treatment if necessary)

Products

MEFLOQUIN TABS 250 MG (AS HCL) (MEPHAQUIN®)

PYRIMETHAMINE WITH SULFADOXINE

Mode of action

Folate antagonists, cause blockade of nucleic acid synthesis in parasite. Sulfadoxine is also a sulfonamide antibacterial.

Indications

Treatment of uncomplicated chloroquine-resistant P. falciparum malaria (usually given with quinine)

Short term prophylaxis of chloroquine-resistant P. falciparum malaria (not recommended)

Contraindications

Allergic reaction to pyrimethamine or sulfonamides

Specific considerations

Folate deficiency anaemia: correct anaemia with calcium folinate; consider risk/benefit if anaemia uncorrected; use of an alternative antimalarial may be preferable.

Pregnancy: Pyrimethamine is a folic acid antagonist; daily supplement of folic acid is required. Sulfonamides cross the placenta and may cause jaundice and haemolytic anaemia in the neonate; ADEC category C.

Breastfeeding: pyrimethamine and sulfadoxine are excreted in breast milk.

Adverse effects

Rare: Stevens–Johnson syndrome, toxic epidermal necrolysis, pulmonary eosinophilia

Dosage

Treatment of uncomplicated chloroquine-resistant P. falciparum malaria

Give as a single dose alone or on day 3 or 4 with oral quinine.
Adult, 3 tablets (75 mg/1500 mg) or 7.5 mL IM.
Child 9–14 years, 2 tablets or 5 mL IM.
Child 4–8 years, 1 tablet or 2.5 mL IM.
Child 1–3 years, half a tablet or 1.25 mL IM.
Infant 6 weeks – 1 year, quarter of a tablet or 0.6 mL IM.

**Patient counselling**
Take tablets with or after food to reduce stomach upset.

**Practice points**
- use quinine plus doxycycline to treat malaria rather than quinine plus pyrimethamine with sulfadoxine
- resistance to pyrimethamine with sulfadoxine may limit its use; combination with quinine is preferred to using it alone
- not recommended for malaria prophylaxis because of toxicity
- take with or after food
- give an additional dose of antimalarial if an oral dose is vomited within 1 hour of administration (or switch to parenteral treatment if necessary)

**Products**
PYRIMETHAMINE TABS 25 MG (DARAPRIM®)

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**05.05 ANTIHELMINTHICS**
See Table 05–07 Anthelmintics comparative information

**05.05.01 Benzimidazoles**

**ALBENDAZOLE**

**Mode of action**
Inhibit microtubule polymerisation and uptake of glucose by binding to beta tubulin in parasite. Other biochemical changes also occur.

**Indications**
Marketed: Roundworm (Ascaris lumbricoides)
Threadworm (Enterobius vermicularis)
Hookworm (Ancylostoma duodenale, Necator americanus)
Whipworm (Trichuris trichiura)
Strongyloides stercoralis
Philippine threadworm (Capillaria philippinensis)
Hydatid cysts (Echinococcus species)
Neurocysticercosis
Beef tapeworm (Taenia saginata)
Pork tapeworm (Taenia solium)
Dwarf tapeworm (Hymenolepis nana)
Cutaneous larva migrans (usually caused by canine or feline hookworm)
Accepted: Some forms of microsporidiosis causing diarrhoea in HIV patients

See also GASTROINTESTINAL in Table 05–01 Drug choice for common infections

**Specific considerations**
Strongyloidiasis in immunosuppressed people: prolonged or recurrent treatment is required, eg repeat course once a month.
Anaemia, dehydration, malnourishment: provide supportive treatment before giving anthelmintic.
Children: Do not use in infants <6 months.
Hepatic impairment: Consider reducing dose for extended treatment, e.g. for hydatid cysts, when used as adjunct to surgery.
Pregnancy: Avoid use; in animal studies albendazole is teratogenic in several species. Until human data are available, it must be suspected of being teratogenic. ADEC category D.
Lactation: Appears safe; albendazole is excreted in breast milk but systemic concentration in mother is low except when used for hydatid disease or neurocysticercosis.

**Adverse effects**
More likely with high dose extended treatment of systemic parasites.
Infrequent: headache, nausea, vomiting, diarrhoea and colic in heavily infected individuals
Rare: itch, paraesthesia, cholestatic jaundice, elevated transaminases, tinnitus, allergic reactions including Stevens–
Johnson syndrome, reversible proteinuria, alopecia, thrombocytopenia, neutropenia

**Dosage**
Roundworm, threadworm, hookworm; take on an empty stomach
Adult, child >6 months and >10 kg, 400 mg single dose.
Child >6 months but <10 kg, 200 mg single dose.
Strongyloidiasis, cutaneous larva migrans, whipworm
Adult, child >6 months and >10 kg, 400 mg daily, for 3 days.
Child >6 months but <10 kg, 200 mg daily, for 3 days.
For strongyloidiasis, repeat after 7 days; treatment is not always successful and may have to be repeated for 1–3 days at intervals of a month, or a longer course given.

**Hydatid disease**
Adult >60 kg, 400 mg twice daily with food.
Adult <60 kg, child >6 years, 7.5 mg/kg twice daily (maximum 400 mg/dose) with food.
Give for 28 days; repeat after 2 weeks for up to 3 cycles.
Neurocysticercosis: Adult, child >6 years, 7.5 mg/kg (maximum 400 mg/dose) twice daily with food, for 8–30 days.
Microsporidiosis: Consult communicable diseases specialist.
Community worm program; take on an empty stomach. Dose every 4-6 months.
Bodyweight >10 kg, 400 mg single dose.
Bodyweight <10 kg, 200 mg single dose.

**Patient counselling**
Tablets may be crushed, chewed or swallowed.

**Practice points**
- Albendazole has a broader spectrum than mebendazole; it is the drug of choice for mixed intestinal worm infection
- Albendazole is used for 1 month before surgery to remove hydatid cysts, or instead of surgery if this is not feasible because access site is difficult, or for multiple cysts
- Ivermectin is preferred treatment if strongyloidiasis is suspected; if this cannot be taken use albendazole
- Corticosteroid cover and antiepileptics may also be required for neurocysticercosis
- Monitor liver function and blood counts during prolonged treatment, eg for hydatid disease
- Albendazole is taken on an empty stomach to minimise absorption when used for intestinal infections and with food to increase absorption when used for systemic infections
- Mixed intestinal nematode infections are relatively common in central and northern Australia; use a single dose of albendazole
- Active against many GI roundworms, where the effect does not depend on human systemic absorption; used in high doses for systemic effect against tissue parasites such as hydatid cysts

**Products**
ALBENDAZOLE TABS 200 MG (CYSTAZOLE®)

**MEBENDAZOLE**

**Mode of action**
Inhibit microtubule polymerisation and uptake of glucose by binding to beta tubulin in parasite. Other biochemical changes also occur.

**Indications**
Marketed: Threadworm (Enterobius vermicularis)
Roundworm (Ascaris lumbricoides)
Hookworm (Ancylostoma duodenale, Necator americanus)
Accepted: Whipworm (Trichuris trichiura)

**Specific considerations**
Strongyloidiasis in immunosuppressed people: prolonged or recurrent treatment is required, eg repeat course once a month.
Anaemia, dehydration, malnourishment: provide supportive treatment before giving anthelmintic.
Children: Do not use in infants <6 months.
Pregnancy: Avoid during first trimester; ADEC category B3.
Breastfeeding: May be used; poorly absorbed by mother.

**Adverse effects**
More likely with high dose extended treatment of systemic parasites.
Infrequent: headache, nausea, vomiting, diarrhoea and colic in heavily infected individuals
Rare: itch, paraesthesia, cholestatic jaundice, elevated transaminases, tinnitus, allergic reactions including Stevens–Johnson syndrome, reversible proteinuria, alopecia, thrombocytopenia, neutropenia

**Dosage**

**Threadworm**
- Adult, child >10 kg, 100 mg as single dose; may repeat after 2–4 weeks.
- Child >6 months and <10 kg, 50 mg as single dose; may repeat after 2–4 weeks.

**Hookworm, roundworm, whipworm**
- Adult, child >10 kg, 100 mg every 12 hours for 3 days.
- Child >6 months and <10 kg, 50 mg every 12 hours for 3 days.

**Patient counselling**
Tablets may be crushed, chewed or swallowed.

**Practice points**
- mixed intestinal nematode infections are relatively common in central and northern Australia; use a single dose of albendazole
- active against many GI roundworms, where the effect does not depend on human systemic absorption; used in high doses for systemic effect against tissue parasites such as hydatid cysts

**Products**

**MEBENDAZOLE SUSP. 100 MG/5 ML 30-60 ML BOTTLE (VERMOX®, BENDAZOLE®)**

**MEBENDAZOLE TABS 100 MG (VERMOX®, BENDAZOLE®, ELMETIN®, THELMOX®, VERMAZOL®)**

**MEBENDAZOLE TABS 500 MG (VERMOX®, BENDAZOLE®)**

**05.05.02 Other anthelmintics**

**NICLOSAMIDE**

**Mode of action**
The activity of niclosamide against worms appears to be due to inhibition of mitochondrial oxidative phosphorylation; anaerobic ATP production is also affected.

**Indications**
Niclosamide is an anthelmintic which is active against most tapeworms, including the beef tapeworm (Taenia saginata), the pork tapeworm (T. solium), the fish tapeworm (Diphyllobothrium latum), the dwarf tapeworm (Hymenolepis nana), and the dog tapeworm (Dipylidium caninum).

**Adverse Effects**
Gastrointestinal disturbances may occur occasionally with niclosamide. Lightheadedness and pruritus have been reported less frequently.

**Dosage**
Niclosamide is given as tablets, which must be chewed thoroughly before swallowing and washed down with water. For infections with pork tapeworm a single 2-g dose is given after a light breakfast. Niclosamide is not active against the larval form (cysticerci) and, although the risk of inducing cysticercosis appears to be theoretical, a laxative is given about 2 hours after the dose to expel the killed worms and minimise the possibility of the migration of ova of T. solium into the stomach; an antiemetic may also be given before treatment.
For infections with beef or fish tapeworms the 2-g dose of niclosamide may be divided, with 1 g taken after breakfast and 1 g an hour later.
In dwarf-tapeworm infections an initial dose of 2 g is given on the first day followed by 1 g daily for 6 days.
Children aged 2 to 6 years are given half the above doses and those under 2 years of age are given one-quarter the above doses.
Unless expulsion of the worm is aided by a laxative, portions are voided in a partially digested form after treatment with niclosamide; the scolex is rarely identifiable.
Niclosamide is used as a molluscicide for the treatment of water in schistosomiasis control programmes.

**Products**

**NICLOSAMIDE TABS 500 MG (YOMESAN®)**
**PRAZIQUANTEL**

**Mode of action**
At low concentrations causes increased muscular activity followed by paralysis of worms, detaching them from host tissue.
At higher concentrations causes integumental damage, which activates host defences to destroy worms (other biochemical changes also occur).

**Indications**
Marketed: Infections due to various types of blood fluke (schistosomiasis)
Accepted: Many tapeworms (cestodes). Neurocysticercosis

**Specific considerations**
Hepatic impairment: Consider reducing dose in significant impairment.
Children: Efficacy in children <2 years is unknown.
Pregnancy: Limited data available; ADEC category B1.
Breastfeeding: Low excretion in breast milk; considered safe.

**Adverse effects**
Usually mild and transitory with short courses.
Common: dizziness, headache, malaise, drowsiness, nausea, vomiting, diarrhoea, anorexia, colic, reversible rises in hepatic transaminases
Rare: Papilloedema, retinal haemorrhages, focal seizures and motor weakness may occur in people treated for neurocysticercosis (due to an intense inflammatory response to dying larvae in CNS).
Skin reactions, eosinophilia and fever are also thought to be host-mediated responses to antigen release during drug-induced worm death.

**Dosage**
Schistosomiasis, 20 mg/kg every 4 hours for 3 doses.
Intestinal tapeworms, 20 mg/kg single dose.
Dwarf tapeworm (Hymenolepis nana), 25 mg/kg as a single dose.
Neurocysticercosis, 50 mg/kg daily in 3 divided doses for 15 days. See Practice points.

**Patient counselling**
Take with food. Swallow with plenty of water to prevent gagging or vomiting due to the bitter taste. Tablet may be cut into halves or quarters, but do not chew.
Praziquantel may increase the effects of alcohol; avoid taking alcohol during your praziquantel course.
Praziquantel may make you feel drowsy or dizzy. If you are affected don't drive or use machinery until 24 hours after finishing your course.

**Practice points**
- corticosteroid cover and antiepileptics may be required for neurocysticercosis
- effective against many tapeworms (cestodes), but roundworms (nematodes) are unaffected

**Products**
PRAZIQUANTIL TABS 600 MG (DISTOCIDE®)
Table 05-01 Drug choice for common infections
The following table is a guide to the choice of anti-infectives for common infections. It is not intended to supplant management advice from clinical microbiologists or infectious diseases specialists.
A drug of choice is listed for each indication. Alternatives are suggested for special situations, eg drug resistance or allergy to penicillins. In general, ampicillin is interchangeable with amoxycillin, flucloxacillin with dicloxacillin and clindamycin with lincomycin. See individual drug monographs for further information.

<table>
<thead>
<tr>
<th>Modifying circumstance</th>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BONE</strong></td>
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<tr>
<td>Compound fractures</td>
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</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>IV flucloxacillin</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV cephalothin or cephalozin or clindamycin</td>
<td>Treat for 1–3 days. If extensive tissue damage and/or devitalised tissue present or contaminated wound, add gentamicin or ciprofloxacin (Gram-negative cover) plus benzylpenicillin or metronidazole (C. perfringens).</td>
</tr>
<tr>
<td>Osteomyelitis, septic arthritis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>adult, child &gt;5, acute infections</td>
<td>S. aureus (methicillin sensitive)</td>
<td>IV then oral flucloxacillin</td>
<td>seek specialist advice</td>
<td>Obtain tissue specimen to identify pathogen; seek specialist advice. Acute infection: give IV for 2–4 weeks, then oral to complete 6 weeks treatment. Chronic infection: give IV for 2–6 weeks, then oral for 3–12 months, depending on duration of symptoms. If prostheses or metal objects remain, treat orally for at least 6–12 months after IV therapy.</td>
</tr>
<tr>
<td>child &lt;5, acute infections</td>
<td>S. aureus (methicillin sensitive)</td>
<td>IV flucloxacillin</td>
<td>seek specialist advice</td>
<td>If not immunised against H. influenzae add cefotaxime or ceftriaxone for 4–6 days, then switch to amoxycillin with clavulanic acid for at least 21 days after IV, otherwise use oral flucloxacillin.</td>
</tr>
<tr>
<td>penicillin allergy, adult and child</td>
<td>S. aureus (methicillin sensitive)</td>
<td>IV cephalothin or cephalozin, then oral cephalexin</td>
<td>IV clindamycin or lincomycin, then oral clindamycin</td>
<td>Obtain tissue specimen to identify pathogen; seek specialist advice. Duration as above. Mild allergy use cefalosporin; severe or immediate allergy use clindamycin or lincomycin.</td>
</tr>
<tr>
<td>adult, child</td>
<td>MRSA</td>
<td>IV vancomycin</td>
<td>seek specialist advice</td>
<td>Continued oral treatment usually required, seek specialist advice.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modifying circumstance</th>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td></td>
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</tr>
<tr>
<td>Endocarditis</td>
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<td></td>
</tr>
<tr>
<td>empirical treatment, native valve</td>
<td>streptococci, S. aureus, E. faecalis</td>
<td>IV benzylpenicillin plus flucloxacillin plus gentamicin</td>
<td>IV vancomycin plus gentamicin</td>
<td>Obtain 3 blood cultures to identify pathogen. Modify treatment as soon as organism and susceptibility are known. Substitute vancomycin for penicillins if infection is hospital-acquired or prosthetic cardiac valve in situ. For enterococci, give gentamicin for 4–6 weeks and benzylpenicillin or ampicillin for 6 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modifying circumstance</th>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td></td>
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</tr>
</tbody>
</table>
### Meningitis

<table>
<thead>
<tr>
<th>Empirical treatment, before hospitalisation</th>
<th>N. meningitidis, S. pneumoniae, L. monocytogenes, H. influenzae</th>
<th>IV benzylpenicillin or IV ceftriaxone plus either IV benzylpenicillin or IV ampicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain blood culture before giving antibiotic if possible.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtain blood culture and lumbar puncture but do not delay antibiotic treatment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If Gram-positive cocci, or in regions or populations with known penicillin-resistant pneumococcus, add vancomycin. Omit penicillins in penicillin allergy and children 3 months – 15 years (Listeria infection unlikely unless immunosuppressed). Give specific therapy once pathogen identified.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>H. influenzae</td>
<td>Oral rifampicin or IM ceftriaxone</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>N. meningitidis</td>
<td>Oral or IM ceftriaxone or oral ciprofloxacin</td>
</tr>
</tbody>
</table>

### Modifying circumstance

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative choice</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EAR, NOSE AND THROAT</strong></td>
<td></td>
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</tr>
</tbody>
</table>

#### Acute bacterial sinusitis

| Severe infection | S. pneumoniae, H. influenzae; less often Moraxella catarrhalis, S. aureus, anaerobes | Oral amoxicillin or doxycycline or amoxicillin with clavulanic acid | Antibiotics not indicated for mild infection. Treat for 7–14 days. If unresponsive to amoxicillin, use amoxicillin with clavulanic acid. |

#### Acute sore throat

| Bacterial | S. pyogenes, but usually viral phenoxyethylpenicillin | Oral erythromycin or roxithromycin | Antibiotics not indicated for mild tonsillitis in communities at low risk of rheumatic fever; treat if highly likely or proven streptococcal or other bacterial infection. Treat for 10 days. Single dose IM benzathine penicillin may be used. |

#### Candidiasis, oral

| C. albicans | Miconazole 2% gel or nystatin suspension | Amphotericin lozenge or suspension | Treat 1–2 weeks. Use oral fluconazole in severe disease, especially in immunocompromised. |

#### Epiglottitis

| Treatment | H. influenzae | IV cefotaxime or ceftriaxone | IV ciprofloxacin | Treat for 5 days. In severe or immediate penicillin allergy use ciprofloxacin. Use prophylaxis regimen to eliminate carrier state. |
| Prophylaxis (contacts) | H. influenzae | Oral rifampicin | IM ceftriaxone | Give rifampicin daily for 4 days or IM ceftriaxone daily for 2 days. |
### Gingivitis

<table>
<thead>
<tr>
<th>Modifying circumstance</th>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>moderate-to-severe</td>
<td>mixed aerobic and anaerobic oral flora</td>
<td>phenoxymethylpenicillin with metronidazole</td>
<td>clindamycin</td>
<td>Debridement is important. Treat for 5 days. For severe acute necrotising disease, start with IV therapy.</td>
</tr>
</tbody>
</table>

### Otitis media

<table>
<thead>
<tr>
<th>Modifying circumstance</th>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute, bacterial</td>
<td>often viral, S. pneumoniae, H. influenzae, B. catarrhalis</td>
<td>oral amoxicillin or amoxycillin with clavulanic acid</td>
<td>cefuroxime or cefaclor</td>
<td>Immediate antibiotic treatment usually unnecessary; use antibiotics if systemic symptoms. Treat for 7–10 days. In penicillin allergy use cefuroxime or cefaclor. If unresponsive to amoxicillin, use amoxycillin with clavulanic acid.</td>
</tr>
</tbody>
</table>

### EYE

#### Bacterial conjunctivitis

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenzae, S. pneumoniae, S. pyogenes, S. aureus</td>
<td>topical chloramphenicol or neomycin plus polymyxin</td>
<td>topical framycetin eye ointment</td>
<td>Treat for 5–7 days. Use ointment at night and drops during the day.</td>
</tr>
</tbody>
</table>

#### Blepharitis

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus, S. epidermidis</td>
<td>framycetin eye ointment</td>
<td>chloramphenicol eye ointment</td>
<td>Apply to lid margins after thorough lid cleansing, until resolved.</td>
</tr>
</tbody>
</table>

#### Herpetic keratitis

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>herpes simplex</td>
<td>aciclovir eye ointment</td>
<td></td>
<td>Treat for at least 7 days. Specialist referral for all new cases or recurrent cases if poor response at 3 days or corneal opacity.</td>
</tr>
</tbody>
</table>

#### Ophthalmic herpes zoster

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>herpes zoster</td>
<td>oral famciclovir or valaciclovir or IV aciclovir</td>
<td></td>
<td>Seek specialist advice. Treat for at least 7 days. Use IV aciclovir if sight threatened. Ensure adequate analgesia.</td>
</tr>
</tbody>
</table>

### GASTROINTESTINAL

#### Acute cholecystitis

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli, Klebsiella spp.</td>
<td>IV ampicillin plus gentamicin</td>
<td>IV cefotaxime or ceftriaxone</td>
<td>Follow with oral amoxicillin with clavulanic acid if necessary. Add metronidazole if there is biliary obstruction.</td>
</tr>
</tbody>
</table>

#### Acute intestinal amoebiasis

<table>
<thead>
<tr>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
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<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
Entamoeba histolytica

**oral** metronidazole plus paromomycin

**oral** tinidazole plus paromomycin

Give metronidazole for 6–10 days; follow with paromomycin (SAS) for 7 days to eradicate pathogenic cysts from GIT (check clearance after treatment). If liver abscess likely seek specialist advice. No treatment needed if organism is E. dispar.

Acute peritonitis

**IV** gentamicin plus ampicillin plus metronidazole or ticarcillin with clavulanic acid alone or piperacillin with tazobactam alone

**IV** metronidazole plus either cefotaxime or ceftriaxone

Metronidazole plus cefotaxime or ceftriaxone has no activity against enterococci. Use IV vancomycin plus gentamicin plus metronidazole in severe or immediate penicillin allergy.

Campylobacter enteritis

**severe** Campylobacter jejuni

oral erythromycin or norfloxacin

Antibacterials unnecessary if mild-to-moderate. Treat with erythromycin for 7–10 days or norfloxacin for 5 days (quinolone resistance is increasingly frequent).

Giardiasis

Giardia lamblia

oral tinidazole

Do not treat asymptomatic carriers unless they handle food. Give tinidazole as single dose (repeat once if necessary); metronidazole for 3–7 days. Use metronidazole in children (oral liquid available).

Peptic ulcer disease

**H. pylori**

see Helicobacter pylori-related ulcers

Pseudomembranous colitis

C. difficile

oral metronidazole

oral bacitracin

Treat for 7–10 days. Oral bacitracin only available from some hospital pharmacies. On specialist advice only use oral vancomycin if unresponsive to metronidazole, or following relapse.

Salmonella infections

**enteritis** Salmonella spp.

oral or IV ciprofloxacin (IV ampicillin if sensitivity confirmed)

IV ceftriaxone

Antibiotics usually unnecessary; not indicated in short term carrier state. Use only if bacteraemia or systemic illness (elderly, neonates, prosthetic valves/grafts are at risk). Treat for at least 5–7 days.

**typhoid, paratyphoid (enteric fever)** Salmonella typhi

ciprofloxacin (oral, IV) or IV ceftriaxone

oral, IV azithromycin or chloramphenicol

Treat for 7–10 days. Follow ceftriaxone with oral amoxycillin, trimethoprim with sulfamethoxazole or chloramphenicol for 14 days.

Shigellosis

Shigella spp.

oral norfloxacin or trimethoprim with sulfamethoxazole

Treat for 5 days. Modify treatment depending on sensitivity results.

Traveller's diarrhoea
<table>
<thead>
<tr>
<th>Condition</th>
<th>Pathogen(s)</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-to-severe E. coli</td>
<td>oral norfloxacin or oral trimethoprim with sulfamethoxazole</td>
<td>Give single dose or treat for 3 days. Mild cases need symptomatic treatment only, eg replacement of fluids.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hookworm, round worm</td>
<td>Ancylostoma duodenale, Necator americanus, Ascaris lumbricoides</td>
<td>albendazole or mebendazole or pyrantel</td>
<td>Give albendazole and pyrantel as single doses; give mebendazole for 3 days.</td>
<td></td>
</tr>
<tr>
<td>Threadworm (pinworm)</td>
<td>Enterobius vermicularis</td>
<td>albendazole or mebendazole or pyrantel</td>
<td>Single dose treatment.</td>
<td></td>
</tr>
<tr>
<td>Strongyloidiasis</td>
<td>Strongyloides stercoralis</td>
<td>albendazole or ivermectin</td>
<td>Give albendazole for 3 days or ivermectin as single dose. Immunocompromised need longer treatment (seek specialist advice).</td>
<td></td>
</tr>
<tr>
<td>Whipworm</td>
<td>Trichuris trichiura</td>
<td>albendazole or mebendazole</td>
<td>Give for 3 days.</td>
<td></td>
</tr>
</tbody>
</table>

**GENITAL**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pathogen(s)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydial and other non-gonococcal infections</td>
<td>C. trachomatis</td>
<td>Give doxycycline for 7 days; azithromycin as single dose. Treat sexual partner(s).</td>
</tr>
<tr>
<td>Donovansis (granuloma inguinale)</td>
<td>Klebsiella granulomatis, azithromycin</td>
<td>Give azithromycin daily for 7 days, or once a week for 4 weeks (or until healed). Treat for syphilis and gonorrhoea if cannot exclude.</td>
</tr>
<tr>
<td>Epididymo-orchitis</td>
<td>N. gonorrhoeae, C. trachomatis, coliforms</td>
<td>oral norfloxacin or trimethoprim or amoxicillin with clavulanic acid or cephalaxin</td>
</tr>
<tr>
<td>Sexually acquired</td>
<td>ceftriaxone plus doxycycline</td>
<td>Give ceftriaxone as single dose, doxycycline for 10–14 days. In areas of low penicillin resistance use amoxicillin plus doxycycline.</td>
</tr>
<tr>
<td>Genital herpes treatment (initial)</td>
<td>herpes, valaciclovir</td>
<td>Treat for 5–7 days.</td>
</tr>
</tbody>
</table>
and recurrent) simplex famciclovir or oral aciclovir

suppression of recurrent infections herpes simplex valaciclovir or famciclovir or oral aciclovir

Treat for up to 6 months. Use only in frequent or severe recurrences (microbiologically proven).

**Gonococcal infection**

<table>
<thead>
<tr>
<th>Uncomplicated</th>
<th>Beta-lactamase producing N. gonorrhoeae</th>
<th>IM ceftriaxone single dose</th>
<th>Treat sexual partner(s). Add empirical treatment for Chlamydia in high risk groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin-sensitive N. gonorrhoeae (uncommon in most regions)</td>
<td>Oral amoxicillin and probenecid</td>
<td>Oral ciprofloxacin or IM ceftriaxone</td>
<td>Treat sexual partner(s). Add empirical treatment for Chlamydia in high risk groups.</td>
</tr>
</tbody>
</table>

**Pelvic inflammatory disease**

<table>
<thead>
<tr>
<th>Sexually acquired, mild-to-moderate</th>
<th>Chlamydia and/or N. gonorrhoeae, subsequently vaginal flora</th>
<th>Oral doxycycline plus either metronidazole or tinidazole plus either ceftriaxone or ciprofloxacin</th>
<th>Give doxycycline and metronidazole for 14 days, ceftriaxone or ciprofloxacin as single dose. In pregnancy or breastfeeding substitute roxithromycin for doxycycline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually acquired, severe</td>
<td>Chlamydia and/or N. gonorrhoeae, subsequently vaginal flora</td>
<td>IV cefotaxime or ceftriaxone plus oral metronidazole plus doxycycline</td>
<td>When symptoms settle, change to oral treatment. See mild-to-moderate above to complete a 14-day course. In pregnancy or breastfeeding substitute roxithromycin for doxycycline.</td>
</tr>
<tr>
<td>Non-sexually acquired, mild-to-moderate</td>
<td>Vaginal flora</td>
<td>Amoxicillin with clavulanic acid plus doxycycline</td>
<td>Treat for 7–10 days. In pregnancy or breastfeeding substitute roxithromycin for doxycycline. For severe infection treat as for sexually acquired, severe (see above).</td>
</tr>
</tbody>
</table>

**Prostatitis**

<table>
<thead>
<tr>
<th>Acute, mild-to-moderate</th>
<th>Urinary tract or sexually transmitted pathogens</th>
<th>Trimethoprim norfloxacin</th>
<th>Treat for 28 days.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute, severe as above</td>
<td>IV ampicillin plus IV gentamicin</td>
<td>Oral ciprofloxacin</td>
<td>Give IV until clinically improved. Complete at least 4 weeks treatment with appropriate oral agent.</td>
</tr>
<tr>
<td>Chronic</td>
<td>Trimethoprim or norfloxacin or ciprofloxacin</td>
<td>Erythromycin or doxycycline</td>
<td>Treatment often ineffective due to poor drug penetration. Use trimethoprim, norfloxacin or ciprofloxacin for 1 month. Try erythromycin or doxycycline for 2–4 weeks if no organism isolated.</td>
</tr>
</tbody>
</table>
### Syphilis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pathogen</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early syphilis (primary, secondary or latent)</td>
<td>Treponema pallidum</td>
<td>IM benzathine penicillin or procaine penicillin oral doxycycline for 14 days. If latent syphilis of &gt;2 years or unknown duration, use benzathine penicillin once a week for 3 doses, or procaine penicillin daily for 15 days. Seek specialist advice for tertiary syphilis.</td>
</tr>
</tbody>
</table>

### Vaginitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pathogen(s)</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial vaginosis (symptomatic)</td>
<td>Gardnerella vaginalis and(or) Mobiluncus spp., other anaerobes</td>
<td>Oral metronidazole or clindamycin vaginal cream oral clindamycin. Use metronidazole for 5 days; clindamycin for 7 days. Avoid using the vaginal cream in pregnancy.</td>
</tr>
<tr>
<td>Trichomoniasis vaginalis</td>
<td>Trichomonas vaginalis</td>
<td>Oral metronidazole or tinidazole. Give tinidazole, metronidazole as single doses except in severe illness, relapse, pregnancy, lactation (use 5-day course of metronidazole). Treat sexual partner(s).</td>
</tr>
</tbody>
</table>

### Vulvovaginal candidiasis

<table>
<thead>
<tr>
<th>Severity</th>
<th>Pathogen</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-moderate</td>
<td>C. albicans</td>
<td>Oral clotrimazole or econazole or miconazole or nystatin. Single dose oral fluconazole after failure of topical treatment. May add topical hydrocortisone for initial treatment. In microbiologically proven recurrent vulvovaginal candidiasis, weekly fluconazole prophylaxis is effective.</td>
</tr>
</tbody>
</table>

### Modifying circumstances

<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Syphilis</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Early syphilis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM benzathine penicillin or procaine penicillin oral doxycycline for 14 days. If latent syphilis of &gt;2 years or unknown duration, use benzathine penicillin once a week for 3 doses, or procaine penicillin daily for 15 days. Seek specialist advice for tertiary syphilis.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaginitis</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gardnerella vaginalis and(or) Mobiluncus spp., other anaerobes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Oral metronidazole or clindamycin vaginal cream oral clindamycin. Use metronidazole for 5 days; clindamycin for 7 days. Avoid using the vaginal cream in pregnancy.</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral metronidazole or tinidazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vulvovaginal candidiasis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>C. albicans</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Oral clotrimazole or econazole or miconazole or nystatin. Single dose oral fluconazole after failure of topical treatment. May add topical hydrocortisone for initial treatment. In microbiologically proven recurrent vulvovaginal candidiasis, weekly fluconazole prophylaxis is effective.</td>
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</tr>
</tbody>
</table>

### MELIOIDOSIS

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkholderia pseudomallei</td>
<td>IV ceftazidime, meropenem or imipenem with oral/IV trimethoprim with sulfamethoxazole; follow with oral trimethoprim with sulfamethoxazole with or without doxycycline for 3–6 months. Lengthy IV treatment sometimes needed; use doxycycline if trimethoprim with sulfamethoxazole not tolerated.</td>
</tr>
<tr>
<td><strong>Modifying circumstance</strong></td>
<td>Common pathogens</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Oral amoxycillin oral clindamycin IV/IM gentamicin plus either IV vancomycin or teicoplanin</td>
</tr>
<tr>
<td>Dental procedures, upper respiratory tract interventions</td>
<td>Oral amoxycillin oral clindamycin IV/IM gentamicin plus either IV vancomycin or teicoplanin</td>
</tr>
<tr>
<td>Genitourinary, GI procedures</td>
<td>IV/IM gentamicin plus IV/IM ampicillin oral clindamycin</td>
</tr>
</tbody>
</table>
Post-exposure prophylaxis (occupational)

needle-stick injury, exposure to body fluids, eg blood

hepatitis B, hepatitis C, HIV

Recurrent rheumatic fever

S. pyogenes IM benzathine penicillin or oral phenoxymethyl-penicillin oral erythromycin IM route preferred. Give benzathine penicillin every 4 weeks or phenoxymethyl-penicillin or erythromycin daily. Seek specialist advice for duration of treatment.

Traveller's diarrhoea

high risk people travelling to high risk countries E. coli oral norfloxacin oral trimethoprim with sulfamethoxazole (use in children) Maximum duration 3 weeks. High risk people include immunocompromised, type 1 diabetes, gastric acid suppression. Advise about avoiding sources of infection.

Modifying circumstance Common pathogens First choice Alternative Additional information

PROPHYLAXIS, SURGICAL

Upper GIT, appendicectomy, biliary or colorectal surgery

Gram-negative aerobes, eg E. coli, Klebsiella spp.; and anaerobes, eg Bacteroides spp.

IV gentamicin or cephalothin or cephazolin plus IV metronidazole IV cefoxitin as single agent Give single dose at induction of anaesthesia. Omit metronidazole in low risk patients where anaerobes unlikely.

Caesarean section

aerobic Gram-negative bacilli, streptococci

IV cephalothin or cephazolin Give mother single dose immediately after clamping the cord.

Hysterectomy, termination of pregnancy

anaerobic bacteria, aerobic Gram-negative bacilli, streptococci

IV cephalothin or cephazolin plus either tinidazole or IV metronidazole IV cefoxitin as single agent Give tinidazole 6–12 hours before surgery; for other drugs, give single dose at induction of anaesthesia.

Oral, nasal, pharyngeal, oesophageal surgery

IV cephalothin or cephazolin Give single dose at induction of anaesthesia. Risk of infection increased in head and neck cancer.

Modifying circumstance Common pathogens First choice Alternative Additional information

RESPIRATORY
Bronchitis

acute infection
usually viral, secondary bacterial
oral amoxycillin or doxycycline

exacerbation of chronic bronchitis
viral, S. pneumoniae, H. influenzae, Moraxella catarrhalis
roxithromycin

Pneumonia, aspiration

aspiration pneumonia and lung abscess, severe
anaerobes, S. milleri
oral amoxycillin or doxycycline

Pneumonia, community-acquired, adult, low risk of death
viral, S. pneumoniae, M. pneumoniae, Chlamydia pneumoniae, Legionella spp., H. influenzae
oral amoxycillin or doxycycline

Pneumonia, community-acquired, adult, moderate risk of death
non-tropical regions and tropical regions if no risk factors for Burkholderia pseudomallei, Acinetobacter baumannii
S. pneumoniae, H. influenzae, Legionella spp., M. pneumoniae, aerobic Gram-negative bacilli
oral amoxycillin or doxycycline

Start with IV therapy, then continue with oral for 7 days total. Add gentamicin if evidence of Gram-negative infection. Use IV cephazolin (and no penicillin) if gentamicin contraindicated. Use moxifloxacin, gatifloxacin or azithromycin in immediate penicillin hypersensitivity.

Pneumonia, community-acquired, adult, high risk of death

tropical regions and risk factors for Burkholderia pseudomallei, Acinetobacter baumannii, eg diabetes, chronic lung or ARDS
IV gentamicin plus ceftriaxone plus either erythromycin or azithromycin

Microbiological results and clinical state determine length of treatment.

Antibacterials are not indicated in viral disease.

Antibacterials indicated only if increased dyspnoea, sputum volume, and sputum purulence. Treat for 5–7 days.

Antibiotics not required for minor degrees. Treat for 7–14 days. On clinical improvement change to oral therapy to complete 7–14 days treatment.

Patient can be safely managed at home; check for worsening illness after 24 hours. Treat for 7 days. Use azithromycin, moxifloxacin or gatifloxacin in immediate penicillin hypersensitivity.
renal disease, alcoholism

Pneumonia, community-acquired, adult, high risk of death

<table>
<thead>
<tr>
<th>Serious illness, non-tropical regions</th>
<th>S. pneumoniae, Legionella spp., S. aureus, M. pneumoniala enteric Gram-negative bacilli</th>
<th>S. pneumoniae, Legionella spp., S. aureus, M. pneumoniala enteric Gram-negative bacilli</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV azithromycin or erythromycin plus benzylpenicillin or gentamicin or single agent IV gatifloxacin or moxifloxacin</td>
<td>Alter treatment according to microbiological results; these and clinical state determine length of treatment. See also Melioidosis.</td>
<td></td>
</tr>
<tr>
<td>Start with IV, then change to oral on significant improvement. Use moxifloxacin or gatifloxacin in immediate penicillin hypersensitivity. Stop gentamicin (or change cefalosporin to benzylpenicillin or ampicillin) after 48 hours if there is no evidence of Gram-negative infection. Microbiological results and clinical state determine length of treatment.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pneumonia, community-acquired, child

<table>
<thead>
<tr>
<th>Age &lt;1 week</th>
<th>Group B Streptococci, Gram-negative enteric bacilli, H influenzae, C. trachomatis</th>
<th>IV benzylpenicillin plus gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat for 7 days.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 week – 4 months

<table>
<thead>
<tr>
<th>Viral, S. pneumoniae, H. influenzae</th>
<th>IV/oral erythromycin or cefotaxime</th>
<th>IV benzylpenicillin or cefotaxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat for 7–14 days. Use erythromycin in mild illness; benzylpenicillin if febrile (or Chlamydia excluded); cefotaxime in severe illness.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4 months – 5 years

<table>
<thead>
<tr>
<th>Viral, S. pneumoniae, H. influenzae</th>
<th>IV benzylpenicillin or cefotaxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat for 7 days. Use benzylpenicillin in moderate illness; cefotaxime or ceftriaxone if it is severe.</td>
<td></td>
</tr>
</tbody>
</table>
ae,
S. aureus
S. pneumoniae, M. pneumoniae
S. pneumoniae, M. pneumoniae, amoxycillin plus roxithromycin (mild illness)
>5 years or ceftriaxone IV benzylpenicillin illin plus roxithromycin (severe illness) Treat for 7 days.

Pneumonia, hospital-acquired
S. pneumoniae, H. influenzae,
Legionella spp., Klebsiella spp. and other coliforms
S. pneumoniae, H. influenzae, Legionella spp., Klebsiella spp. and other coliforms, P. aeruginosa
amoxycillin with clavulanic acid
IV benzylpenicillin illin plus gentamicin or cephazolin

Pneumonia, staphylococcal
S. aureus
IV flucloxacillin
Treat for up to 4–6 weeks. Use IV vancomycin for MRSA.

Modifying circumstance Common pathogens First choice Alternative Additional information

SEPTICAEMIA

Empirical treatment, no obvious source of infection

febrile neutropenic patient, high risk,
neutrophils <0.5x10⁹/L

Gram-positive or Gram-negative organisms, P. aeruginosa

IV gentamicin plus either ceftazidime or cefepime or cefpirome or piperacillin with tazobactam or ticarcillin with clavulanic acid

Recommendations do not apply to HIV patients. Antibiotic choice depends on local susceptibility patterns. Use IV cefalosporin alone in low risk people. Add vancomycin if MRSA or other Gram-positive resistant organism proven or suspected.
or cephalothin

3 months IV ampicillin plus gentamicin; 4 months –

4 years IV benzylpenicillin; >4 years IV benzylpenicillin plus flucloxacillin

These regimes assume that meningitis has been excluded.

Empirical treatment, source of infection: skin (including cellulitis)

<table>
<thead>
<tr>
<th>Immune competent child</th>
<th>Immune competent adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 months IV ampicillin plus gentamicin; 4 months – 4 years IV benzylpenicillin; &gt;4 years IV benzylpenicillin plus flucloxacillin</td>
<td></td>
</tr>
</tbody>
</table>

S. aureus, S. pyogenes IV flucloxacillin or cephalothin or cephazolin or clindamycin If clearly due to S. pyogenes alone, use IV benzylpenicillin.

Source of infection: skin, infected decubitus and ischaemic ulcers and diabetic foot infections

S. aureus, enteric Gram-negative rods, anaerobes, beta-haemolytic streptococci IV flucloxacillin plus metronidazole plus gentamicin ticarcillin with clavulanic acid plus gentamicin Substitute cephalothin or cephazolin for flucloxacillin in penicillin allergy. If an aminoglycoside is contraindicated consider ciprofloxacin.

Modifying circumstance Common pathogens First choice Alternative Additional information

**SKIN AND SOFT TISSUE**

**Acne**

<table>
<thead>
<tr>
<th>Moderate</th>
<th>Common pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propionibacterium acnes</td>
<td>doxycycline or topical clindamycin or erythromycin</td>
</tr>
</tbody>
</table>

Use with topical retinoid or keratolytic. Try to limit oral antibiotics to 6 months and topical antibiotics to 3 months.

**Bites (human and animal) and clenched fist injuries**

Clean and debride wound thoroughly. Give IM benzylpenicillin if treatment will be delayed. Treat for 5 days for prevention and 5–10 days for treatment of established infection (unless osteomyelitis is possible).
patients requiring IV treatment

IV ticarcillin with clavulanic acid

Treat for 7–14 days. Switch to oral amoxicillin with clavulanic acid when symptoms settle.

Cellulitis and erysipelas

mild-to-moderate infection

S. pyogenes, S. aureus

IM procaine penicillin or phenoxymethylpenicillin

oral cephalaxin or clindamycin

If S. aureus is suspected or proven, use flucloxacillin. Use IV therapy in severe disease.

Coral cuts

mild-to-moderate infection

S. pyogenes, Vibrio spp., Aeromonas hydrophila

phenoxymethylpenicillin or roxithromycin or oral erythromycin or IM benzathine penicillin

Treat for 10 days oral therapy or single dose benzathine penicillin. If primary pathogen S. aureus use flucloxacillin. If marine pathogen suspected use ciprofloxacin plus phenoxymethylpenicillin.

Cutaneous candidiasis

C. albicans

topical clotrimazole, econazole, miconazole or nystatin

topical terbinafine

Continue treatment with topical azoles or nystatin for 2 weeks after symptoms resolve.

Diabetic foot infections, varicose or decubitus ulcers with cellulitis

mild infections

anaerobes, Gram-positive and Gram-negative aerobes (mixed infection)

oral metronidazole and cephalaxin

oral amoxicillin with clavulanic acid

Duration depends on clinical response. If severe infection use single agent IV ticarcillin with clavulanic acid or clindamycin plus oral ciprofloxacin, gatifloxacin or moxifloxacin.

Folliculitis, boils, carbuncles

extensive lesions or systemic symptoms

S. aureus

oral flucloxacillin

oral cephalaxin or clindamycin

Treat for 5–7 days.

Impetigo

S. aureus

topical mupirocin (mild infection)

flucloxacillin or cephalaxin or clindamycin (severe infection)

Remove crusts twice a day. Treat topically for 7 days; orally for 10 days (oral antibiotics active against S. pyogenes).

S. pyogenes

phenoxymethylpenicillin or single dose benzathine penicillin

cephalaxin or erythromycin

Remove crusts twice a day. Treat for 10 days.

Mastitis
mild-to-moderate S. aureus oral fluclocoxacillin oral cephalaxin or clindamycin Treat for 5–7 days. Start with IV fluclocoxacillin, cephalothin or cephalaxin if severe. In severe penicillin allergy use clindamycin, lincomycin or vancomycin.

Paronychia

acute S. aureus oral fluclocoxacillin oral cephalaxin or clindamycin Treat for 7 days. Consider possibility of herpetic whitlow.

chronic C. albicans topical clotrimazole, econazole, miconazole or nystatin oral fluconazole or itraconazole If poor response to topical therapy treat orally for at least 2 weeks. Add topical corticosteroid if inflammation present. Protect hands from excessive water.

Scabies, infected

secondary bacterial infection S. pyogenes phenoxymethylpenicillin or oxithromycin or oral erythromycin or IM benzathine penicillin Treat for 10 days oral therapy or single dose benzathine penicillin. Treat scabies concurrently.

Tinea capitis

Trichophyton, Microsporum, Epidermophyton oral griseofulvin or oral terbinafine or itraconazole Treat for 4–8 weeks.

Tinea corporis, pedis, cruris

Trichophyton, Microsporum, Epidermophyton topical clotrimazole, econazole, miconazole or ketoconazole oral griseofulvin, terbinafine or itraconazole Treat for 2 weeks after symptoms resolve. If response to topical treatment poor, use griseofulvin (4 weeks), terbinafine (2–6 weeks) or itraconazole (2–4 weeks).

Tinea unguium (onychomycosis) (see Nail infections)

Trichophyton, Microsporum, Epidermophyton oral terbinafine or amorolfine nail lacquer oral griseofulvin or itraconazole Give terbinafine for 6 weeks (fingernails) or 12 weeks (toenails). Give amorolfine for 6 months (fingernails) or longer (toenails). Give griseofulvin for 4–6 months; itraconazole for 3 months.

Trauma, crush injuries, stab wounds

S. aureus, S. pyogenes, C. perfringens and aerobic Gram-negative bacilli IV fluclocoxacillin plus gentamicin plus metronidazole IV cephalothin or cephalaxin plus metronidazole Treat for at least 5 days. If hospitalisation unnecessary and antibiotics indicated, use oral fluclocoxacillin plus metronidazole for 5–7 days or amoxycillin with clavulanic acid alone.
<table>
<thead>
<tr>
<th>Modifying circumstance</th>
<th>Common pathogens</th>
<th>First choice</th>
<th>Alternative</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>URINARY</strong></td>
<td></td>
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<tr>
<td>Acute cystitis</td>
<td></td>
<td>oral trimethoprim or cephalexin</td>
<td>oral amoxycillin with clavulanic acid or nitrofurantoin</td>
<td>Treat females for 3–5 days (7–10 days if pregnant); males for 14 days; children for 5 days, then prophylaxis until investigated. Investigate all males. For proven multi-resistance use norfloxacin. For proven susceptible organisms use amoxycillin. Trimethoprim with sulfamethoxazole is an alternative in children. If treatment fails consider resistance, reinfection, anatomical abnormality; seek specialist advice.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV ampicillin plus gentamicin</td>
<td>IV cefotaxime or ceftriaxone (no enterococci cover) or ciprofloxacin</td>
<td>Usually treat for 14 days. Start with IV therapy, complete with oral (change early in mild-to-moderate infection). May use gentamicin alone in penicillin allergy; add urinary alkaliniser to maintain urinary pH &gt;8. If gentamicin contraindicated use cefotaxime or ceftriaxone. Reserve ciprofloxacin for suspected or proven pseudomonal infections. For mild infections use cephalexin. For alternatives, see <strong>Acute cystitis</strong>.</td>
</tr>
<tr>
<td>Relapsing UTIs</td>
<td></td>
<td>trimethoprim or amoxycillin with clavulanic acid or cephalaxin or nitrofurantoin</td>
<td>norfloxacin</td>
<td>For acute infection treat for 10–14 days. Use norfloxacin only if resistant to all other agents. Usually indicates chronic prostatitis in males.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cephalaxin, trimethoprim or nitrofurantoin</td>
<td></td>
<td>Give at night for 3–6 months or longer. Postcoital single dose cephalaxin, trimethoprim or nitrofurantoin may be an alternative to long term prophylaxis.</td>
</tr>
</tbody>
</table>
Table 05-02 Aminoglycosides comparative information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Adverse reactions</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ototoxicity</td>
<td>ototoxicity</td>
<td>nephrotoxicity</td>
<td>neuromuscular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(vestibular)</td>
<td>(cochlear)</td>
<td></td>
<td>blockade</td>
</tr>
<tr>
<td>amikacin</td>
<td>broadest spectrum; use for organisms resistant to gentamicin and tobramycin</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>gentamicin</td>
<td>aminoglycoside of choice for most hospital-acquired Gram-negative infections</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>streptomycin</td>
<td>second line agent for tuberculosis similar activity to gentamicin;</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>tobramycin</td>
<td>slightly more active against Pseudomonas spp. in vitro</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 05-03 Classification of antiviral drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Primary indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>guanine analogues</td>
<td>aciclovir, famciclovir</td>
<td>herpes simplex, shingles</td>
</tr>
<tr>
<td></td>
<td>valaciclovir</td>
<td>herpes simplex, shingles, CMV</td>
</tr>
<tr>
<td></td>
<td>ganciclovir, valganciclovir</td>
<td>CMV</td>
</tr>
<tr>
<td>neuraminidase inhibitors</td>
<td>oseltamivir, zanamivir</td>
<td>influenza A and B</td>
</tr>
<tr>
<td></td>
<td>adefovir</td>
<td>hepatitis B</td>
</tr>
<tr>
<td></td>
<td>cidofovir, foscarnet</td>
<td>CMV</td>
</tr>
<tr>
<td>other antivirals</td>
<td>palivizumab, ribavirin</td>
<td>respiratory syncytial virus</td>
</tr>
<tr>
<td></td>
<td>(peg)interferon alfa</td>
<td>hepatitis B, hepatitis C</td>
</tr>
<tr>
<td></td>
<td>ribavirin with peginterferon alfa</td>
<td>hepatitis C</td>
</tr>
</tbody>
</table>

Table 05–04 Antitubercular drugs comparative information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activity against M. tuberculosis</th>
<th>Pregnancy</th>
<th>Lactation</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethambutol</td>
<td>slowly bacteriostatic</td>
<td>may be used</td>
<td>may be used</td>
<td>safe to use in children &gt;6 years</td>
</tr>
<tr>
<td>isoniazid</td>
<td>bactericidal</td>
<td>may be used</td>
<td>may be used</td>
<td>safe to use</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>bactericidal; active within macrophage</td>
<td>may be used</td>
<td>contact specialised information service</td>
<td>limited experience</td>
</tr>
<tr>
<td>rifampicin</td>
<td>rapidly bactericidal; intracellular activity</td>
<td>may be used</td>
<td>may be used</td>
<td>safe to use</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptomycin</td>
<td>bactericidal</td>
<td>avoid use</td>
<td>may be used</td>
<td>safe to use</td>
</tr>
<tr>
<td>capreomycin</td>
<td>bacteriostatic</td>
<td>seek specialist</td>
<td>limited information</td>
<td>limited</td>
</tr>
<tr>
<td>Drug</td>
<td>Daily dose</td>
<td>3 times a week dose</td>
<td>Twice a week dose</td>
<td>Duration of treatment</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------------------</td>
<td>------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>isoniazid</td>
<td>adult, 5 mg/kg (maximum 300 mg)</td>
<td>adult, 15 mg/kg (maximum 600 mg)</td>
<td>adult, 15 mg/kg (maximum 900 mg)</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>child, 10 mg/kg (maximum 300 mg)</td>
<td>child, 20–30 mg/kg (maximum 600 mg)</td>
<td>child, 20–30 mg/kg (maximum 900 mg)</td>
<td></td>
</tr>
<tr>
<td>rifampicin</td>
<td>adult, child, 10 mg/kg (maximum 600 mg)</td>
<td>adult, child, 15 mg/kg (maximum 600 mg)</td>
<td>adult, child, 15 mg/kg (maximum 900 mg)</td>
<td>6 months</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>adult, 20–25 mg/kg (maximum 2 g)</td>
<td>adult, 50 mg/kg (maximum 3 g)</td>
<td>adult, 70 mg/kg (maximum 4 g)</td>
<td>first 2 months only</td>
</tr>
<tr>
<td></td>
<td>child, 15–30 mg/kg (maximum 2 g)</td>
<td>child, 50 mg/kg (maximum 2 g)</td>
<td>child, 50 mg/kg (maximum 2 g)</td>
<td></td>
</tr>
<tr>
<td>ethambutol</td>
<td>adult, child &gt;6 years, 15–20 mg/kg (maximum 1.6 g)</td>
<td>adult, child &gt;6 years, 25–30 mg/kg (maximum 2.4 g)</td>
<td>adult, child &gt;6 years, 45 mg/kg (maximum 4 g)</td>
<td>first 2 months only</td>
</tr>
<tr>
<td>pyridoxine</td>
<td>25 mg daily</td>
<td>25 mg 3 times a week</td>
<td>25 mg twice a week</td>
<td>concurrent with isoniazid</td>
</tr>
</tbody>
</table>

**Table 05–06 Anthelmintics comparative information**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy</th>
<th>Lactation</th>
<th>Children</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzimidazoles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>albendazole</td>
<td>avoid use</td>
<td>may be</td>
<td>safe to use in children &gt;6 months</td>
<td>well tolerated</td>
</tr>
<tr>
<td>mebendazole</td>
<td>avoid use in first trimester</td>
<td>may be used</td>
<td>safe to use in children &gt;6 months</td>
<td>well tolerated</td>
</tr>
<tr>
<td><strong>Other anthelmintics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ivermectin</td>
<td>avoid use</td>
<td>may be</td>
<td>safe to use in children &gt;5 years and/or &gt;15 kg</td>
<td>mild adverse effects when used for strongyloidiasis</td>
</tr>
<tr>
<td>praziquantel</td>
<td>may be used</td>
<td>may be</td>
<td>safe to use in children &gt;2 years</td>
<td>well tolerated in short courses</td>
</tr>
<tr>
<td>pyrantel</td>
<td>avoid use in first trimester</td>
<td>may be used</td>
<td>safe to use</td>
<td>well tolerated</td>
</tr>
</tbody>
</table>
CHAPTER 06 ENDOCRINE SYSTEM

06.01 DRUGS USED IN DIABETES

DIABETES
Diabetes is classified as type 1 diabetes (previously referred to as insulin-dependent diabetes mellitus, IDDM); type 2 diabetes (previously referred to as non–insulin-dependent diabetes mellitus, NIDDM); gestational diabetes and other specific types, eg secondary to endocrine disorders or pancreatic disease. Only type 1 and type 2 diabetes are discussed here.

Prevention of diabetes
Lifestyle changes (diet improvement, weight reduction and increase in physical activity) delay onset of type 2 diabetes in people with impaired glucose tolerance. Consider screening for diabetes in patients with hypertension, hyperlipidaemia, obesity, family history of diabetes or history of gestational diabetes. Diabetes is a strong risk factor for cardiovascular disease. Other risk factors for cardiovascular disease such as smoking, hypertension, obesity, and hyperlipidaemia should be addressed. The use of an ACE inhibitor, of low-dose aspirin and of a lipid-regulating drug can be beneficial in patients with diabetes and a high risk of cardiovascular disease.

Rationale for drug use

Before starting treatment
Insulin treatment may be required in an emergency, especially in children, because of risk of fatal ketoacidosis. In type 2 diabetes, develop a healthy eating plan and exercise/activity program; there should be a 3-month trial before considering drug treatment. Plan appropriate investigations and assessment (renal function, eye examination). Assess risk factors for cardiovascular complications (smoking, hypertension, dyslipidaemia, obesity). Consider referrals to dietitian, diabetes educator, endocrinologist, podiatrist and ophthalmologist.

Drug choice
Two large controlled trials, The Diabetes Control and Complications Trial (DCCT) in people with type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) in people with type 2 diabetes, showed that tight blood glucose control reduces risk of diabetes-related microvascular complications, eg retinopathy and nephropathy. It may have a beneficial effect on the risk of macrovascular complications. Contrary to previous results in people with type 2 diabetes, sulfonylureas or insulin did not increase cardiovascular morbidity and mortality.

Type 1 diabetes
Insulin is a lifelong treatment. Intensive treatment reduces the risk of microvascular complications but with a greater risk of hypoglycaemia and weight gain. An intensive regimen cannot be used in young children because of possible long term adverse effects of hypoglycaemia on cerebral development. Continuous SC insulin infusion has similar or better efficacy than intensive regimens with multiple injections.

Type 2 diabetes
Antidiabetic treatment is not a substitute for a healthy diet and exercise, which should always be encouraged. Consider antidiabetic treatment:
- if appropriate glycaemic control is not achieved after a 3-month period of healthy eating and regular exercise/activity
- when severe symptoms are present or blood glucose concentrations are consistently >20 mmol/L.
In non-obese patients consider sulfonylureas or metformin first. In the UKPDS study, glibenclamide significantly reduced the incidence of diabetes-related events in non-obese patients; however, it has a higher risk of hypoglycaemia compared to other sulfonylureas. Equivalent long term efficacy data are not available for other sulfonylureas. Insulin has a similar efficacy but a greater risk of hypoglycaemia and weight gain than sulfonylureas. In obese patients consider metformin first as it significantly reduces the incidence of diabetes-related events and
Efficacy of a single oral antidiabetic drug will decline over time (secondary failure); substitution of one oral drug for another does not usually improve glucose control. When a first line treatment fails, there is currently no alternative with proven long term benefits. Sulfonylurea with metformin is the most widely used combination. There is controversial evidence that this combination may increase risk of diabetes-related and all-cause mortality. Addition of bedtime isophane insulin to oral treatment (metformin, sulfonylurea or metformin with sulfonylurea combination) reduces glycated haemoglobin similarly to multiple daily insulin injections but with a smaller weight increase. Further data are required to define the best combinations of antidiabetic treatments.

Acarbose, repaglinide and thiazolidinediones have only been assessed in terms of blood glucose control; long term comparative trials with morbidity and mortality outcomes are required to define their role in diabetes treatment.

**Sulfonylureas**
Include glibenclamide, gliclazide, glimepiride and glipizide.
Risk of weight gain.
Risk of hypoglycaemia, particularly in the elderly and in people with renal or hepatic impairment; avoid use of glibenclamide in these people.

**Metformin**
No risk of hypoglycaemia when used alone.
Metformin is the drug of first choice in overweight patients in whom strict dieting has failed to control diabetes, if appropriate it may also be considered as an option in patients who are not overweight. It is also used when diabetes is inadequately controlled with sulphonylurea treatment.
GI adverse effects can occur; may be reduced by titrating slowly.
Lactic acidosis is the most serious adverse effect but is rare (0.03 cases per 1000 patient years); occurs mainly with high dose and in people with renal impairment (including situations with a risk of altered renal function, eg dehydration, severe infection, ketoacidosis, surgery, use of iodinated contrast media), hepatic impairment, alcohol misuse, old age and heart failure.

**Acarbose**
Less effective than sulfonylureas and metformin; it has a small but significant effect in lowering blood glucose; may be used as monotherapy or with sulfonylurea, metformin (increased GI adverse effects) or insulin.
GI adverse effects (diarrhoea, flatulence) can occur, particularly at start of treatment; may be reduced by starting on low dose and titrating slowly.
Hypoglycaemia may occur in combination with sulfonylureas, repaglinide or insulin; give glucose but not sucrose (cane sugar) because of delayed absorption of sucrose.
Flatulence deters some from using acarbose although this side-effect tends to decrease with time.

**Repaglinide**
May be used as monotherapy; no improvement expected in patients who have been inadequately controlled with sulfonylureas.
Risk of hypoglycaemia seems similar to that with sulfonylureas.
Limited data evaluating combinations with other oral antidiabetic drugs exist; combination with metformin or insulin may improve glycaemic control but at increased risk of hypoglycaemia.

**Thiazolidinediones**
Include rosiglitazone and pioglitazone.
Rosiglitazone and pioglitazone are currently marketed for use as monotherapy or in combination with sulfonylureas or metformin or insulin. However, there are no adequate comparative data on clinical outcomes with either metformin or sulfonylureas that could justify their use as monotherapy. It should be noted that in European countries combination with insulin is contraindicated because of increased risk of heart failure.
Up to one-third of patients do not respond to thiazolidinediones; combinations of a thiazolidinedione plus either metformin or a sulfonylurea seem to control blood glucose similarly to metformin with a sulfonylurea but are not better tolerated.
Insulin, alone or with metformin or a sulfonylurea, has a better benefit to risk ratio than triple therapy of a thiazolidinedione with metformin and a sulfonylurea.
Weight increase and oedema are common adverse effects of thiazolidinediones. Caution is required in patients with heart failure or at risk of heart failure.
Hepatotoxicity may occur with rosiglitazone and pioglitazone; close monitoring of liver enzymes is required.

**Insulin**
May be used with oral antidiabetic drugs in type 2 diabetes or as monotherapy.
Risk of weight gain and hypoglycaemia.
Control of other risk factors
Controlling other vascular risk factors, in particular smoking, hypertension, obesity and dyslipidaemia, may be more important than tight glycaemic control in decreasing diabetes-related morbidity and mortality.

**Hypertension**
Reducing BP decreases diabetes-related complications and mortality; aim to keep BP <130/85 mm Hg.

**Microalbuminuria**
Improvement in glycaemic control and reduction of BP reduces progression of renal disease.
ACE inhibitors delay microalbuminuria in hypertensive patients and reduce progression of microalbuminuria to overt nephropathy in normotensive patients. Losartan and irbesartan reduce progression of renal disease in patients who have type 2 diabetes with hypertension and proteinuria; irbesartan is also approved for use when microalbuminuria is present.

**Cardiovascular disease prevention**
Low dose aspirin is recommended in patients at high risk of cardiovascular disease; its benefit may be offset by risk of GI adverse effects in diabetic patients without other cardiovascular risk factors.
Ramipril reduces risk of MI, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients >55 years with one or more risk factors. Consider using statins in patients with LDL >3.4 mmol/L or with cardiovascular disease.

**Special cases**
Pregnancy: Tell patient to seek advice several months before planned conception to optimise glucose control. Tight blood glucose control, especially at the time of conception and early in pregnancy, reduces risk of spontaneous abortion and congenital malformations. Replace oral antidiabetic drugs with insulin (insulin may also be required in gestational diabetes).

**Treatment endpoints**
Adjust treatment endpoints individually; intensive treatment may be inappropriate, eg when risk of (and from) hypoglycaemia is unacceptable, in presence of severe concomitant disease, in children, adolescents and the very elderly.
Ideal treatment endpoints proposed by the Australian Diabetes Society:
- fasting blood glucose, <6 mmol/L
- random blood glucose, 4–8 mmol/L
- glycated haemoglobin concentration (HbA1c), 7% (or less).

**Monitoring**

**Blood glucose self-monitoring**
Useful to identify and treat hyperglycaemia and hypoglycaemia and to adjust insulin dosage
- Blood glucose meters give more accurate reading than visual strips, but are more expensive.
- Frequency and pattern of monitoring depends on clinical situation; consider referral to diabetes educator to plan a self-monitoring schedule:
  - in people on an intensive insulin regimen, advise monitoring 4 times daily, ie before each meal and at bedtime; postprandial monitoring may also be useful
  - whether self-monitoring is useful in people with type 2 diabetes who are not treated with insulin is controversial; monitoring may be considered at different times of the day 1–2 days a week; may be useful when HbA1c suggests poor control, during the 2 weeks before a clinic visit or when symptoms are suggestive of hyper- or hypoglycaemia
  - monitor more frequently during illness or stress and after changes in treatment.

**Ketone self-monitoring**
Essential for identification of impending ketoacidosis in type 1 diabetes; blood glucose concentrations may be deceptively normal during illness with severe ketonuria.
Most commonly performed on urine; blood ketone testing is also possible with some blood glucose meters.
Advise monitoring when symptoms of ketoacidosis are present, during acute illness or stress, with persistent high glucose concentrations (>15 mmol/L), or in pregnant women with pre-existing type 1 diabetes.

**Glycated haemoglobin**
Glycated haemoglobin indicates glycaemic control during preceding 2–3 months; there is a continuous relationship between the risk of microvascular complications and level of glycated haemoglobin.
Monitor glycated haemoglobin every 3–6 months.
Glycated haemoglobin results vary between laboratories; use the same laboratory for repeated testing.
Drugs affecting blood glucose
Many drugs affect blood glucose concentration and may alter control of diabetes or increase risk of hypoglycaemia when used with insulin or oral antidiabetic drugs.

Drugs which may decrease blood glucose concentration: aspirin (analgesic doses), disopyramide, octreotide, pentamidine, perhexiline, quinine, quinolones.

Drugs which may increase blood glucose concentration: adrenaline, arsenic trioxide, baclofen, beta2 agonists (high dose, eg IV salbutamol), busulfan (high dose), chlorpromazine, clozapine, combined oral contraceptives, colaspase, cyclosporin, diazoxide, fludarabine, glucocorticoids, haloperidol, HRT, interferon alfa, isoniazid, isotretinoin, nicotinic acid (lipid-lowering doses), octreotide, olanzapine, pentamidine, phenytoin, PIs, quetiapine, quinolones, risperidone, somatropin, tacrolimus, TCAs, thiazide diuretics (high dose).

When introducing or withdrawing a drug that influences blood glucose concentration, close monitoring of blood glucose and adjustment of insulin or antidiabetic drug dosage are required.

Alcohol: decreases blood glucose concentration by inhibiting hepatic glucose output; increases risk of hypoglycaemia and can also mask its warning symptoms. Limit alcohol intake and take food with alcohol.

Beta-blockers: may mask some hypoglycaemic warning symptoms and increase incidence and severity of hypoglycaemia but data are conflicting; choose beta1 selective beta-blockers, such as atenolol, which has been shown to be safe and effective in patients with type 2 diabetes.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis is caused by absolute or relative lack of insulin; it may occur at the onset of type 1 diabetes or during intercurrent illness.

Prevention of ketoacidosis in type 1 diabetes
Patients should monitor their urine ketones when symptoms of ketoacidosis are present (eg nausea, vomiting, weakness, rapid breathing, sweet breath odour), during acute illness or stress, and when persistent high blood glucose concentrations are present (>15 mmol/L).

Give patients an emergency contact number and an individualised sick day management plan:
- monitor blood glucose frequently (at least 3–4 times daily, and as often as every hour)
- increase insulin dosage according to blood glucose monitoring
- do not stop insulin even if not eating
- monitor urine ketones, particularly when blood glucose is >15 mmol/L (blood ketone testing is available with some blood glucose meters)
- sip sweetened fluids frequently if not able to tolerate solid food
- seek medical advice when persistent urine ketones and high glucose concentrations are present, or if repeated vomiting occurs.

Treatment of ketoacidosis
Fluid and electrolyte replacement: start fluid replacement with IV infusion of sodium chloride 0.9%; adjust dosage of potassium chloride according to plasma potassium concentrations; sodium chloride 0.45% can then be used if corrected serum sodium is normal or elevated. Use sodium bicarbonate only in cases of extreme acidosis and/or shock.

Insulin: blood glucose concentration should be reduced slowly. Give short acting insulin by IV infusion at a rate of 5–10 units/hour in adults and 0.1 units/kg/hour in children (diluted to 1 unit/mL in sodium chloride 0.9%). Dosage may need to be decreased, especially in young children, when blood glucose has fallen to 10 mmol/L. Intermittent IM injection is an alternative only if circulatory state is satisfactory. Begin glucose infusion once blood glucose has fallen to 10–15 mmol/L, while continuing insulin infusion until urine ketones are no longer detectable.

Treatment of hyperosmolar hyperglycaemic non-ketotic coma
Occurs mainly in elderly people with type 2 diabetes. Infection is the most common precipitating factor. Clinical management is broadly similar to management of diabetic ketoacidosis. Use sodium chloride 0.45% for fluid and electrolyte replacement. Lower insulin dosage than for diabetic ketoacidosis has been recommended (0.01–0.05 units/kg/hour).

06.01.01 Insulin’s

Mode of action
Increase or restore ability to metabolise glucose by enhancing cellular glucose uptake; inhibit endogenous glucose output and lipolysis.

Comparative information
Origin
Available preparations are either purified bovine insulins or human insulins obtained by recombinant DNA
technology; initial concern about reduced awareness of hypoglycaemia with human insulin has not been confirmed.

Onset and duration of action
See Table 06-1 Insulins: comparative information
Ultra-short and short acting insulins are soluble insulins (clear solution).
Insulin lispro and insulin aspart are human insulin analogues; their ultra-short onset of action allows them to be given
immediately before meals.
Intermediate acting insulins (cloudy solution) have a prolonged duration of action (eg isophane insulin).
Mixed insulins (also called biphasic insulins) combine a short or ultra-short acting insulin in varying proportions
(20–50%) with an intermediate acting insulin.
Insulin glargine (clear solution) is a human insulin analogue which provides a constant basal insulin level over
24 hours allowing for once-daily dosing.

Safety
Ultra-short acting insulins seem to reduce the frequency of severe hypoglycaemia compared to short acting insulin
but evidence is limited.
There is some evidence of decreased nocturnal hypoglycaemia with insulin glargine compared to once daily isophane
insulin in patients with type 2 diabetes. Insulin glargine is more painful to inject than isophane insulin. Post-
marketing surveillance data are required to monitor local reactions as some animal studies have identified risk of
local toxicity.

Presentation
All preparations contain 100 units/mL and are suitable for SC injection. Short acting insulins and insulin lispro can
be given IV, eg in diabetic ketoacidosis.
Most preparations are available in vials for use with a syringe (0.3 mL, 0.5 mL or 1 mL). Most ultra-short, short and
intermediate acting human insulins are also available in cartridges for use with a pen injection device. Pen devices
are more convenient than syringes and avoid the need to draw up insulin. Some preparations are available as
disposable pen devices.
Examples of recommended insulin regimens
- Short-acting insulin mixed with intermediate-acting insulin: twice daily (before meals)
- Short-acting insulin mixed with intermediate-acting insulin: before breakfast
- Short-acting insulin: before evening meal
- Intermediate-acting insulin: at bedtime
- Short-acting insulin: three times daily (before breakfast, midday, and evening meal)
- Intermediate-acting insulin: at bedtime
- Intermediate-acting insulin with or without short-acting insulin: once daily either before breakfast or at
bedtime suffices for some patients with type 2 diabetes who need insulin, sometimes in combination with
oral hypoglycaemic drugs

06.01.01.01 Short-acting insulin’s

Products
INSULIN, HUMAN, SOLUBLE VIAL 100 IU/ML 10 ML VIAL (HUMULIN R®, GENSULIN R®,
ACTRAPID®)

06.01.01.02 Intermediate-acting insulin’s
06.01.01.03 Long-acting insulin’s
Insulin glargine should be available as an option for patients with type 1 diabetes. Insulin glargine is not recommended for routine use in patients with type 2 diabetes who require insulin, but it may be considered in type 2 diabetes for those:

- who require assistance with injecting their insulin; or
- whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia; or
- who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.

Products
INSULIN, HUMAN, GLARGINE, RECOMBINANT HUMAN INSULIN ANALOGUE 100 IU/ML (LANTUS®)

06.01.02 Oral antidiabetic drugs
Oral antidiabetic drugs are used for the treatment of type 2 (non-insulin-dependent) diabetes mellitus. They should be prescribed only if the patient fails to respond adequately to at least 3 months’ restriction of energy and carbohydrate intake and an increase in physical activity. They should be used to augment the effect of diet and exercise, and not to replace them.

06.01.02.01 Sulfonylureas
The sulfonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulphonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital. Sulphonylureas are considered for patients who are not overweight, or in whom metformin is contra-indicated or not tolerated. Several sulphonylureas are available and choice is determined by side-effects and the duration of action as well as the patient’s age and renal function. The long-acting sulphonylureas like glibenclamide is associated with a greater risk of hypoglycaemia; for this reason they should be avoided in the elderly and shorter-acting alternatives, such as gliclazide, should be used instead. Chlorpropamide also has more side-effects than the other sulphonylureas (see below) and therefore it is no longer recommended.

When the combination of strict diet and sulphonylurea treatment fails other options include:

- combining with metformin (reports of increased hazard with this combination remain unconfirmed);
- combining with acarbose, which may have a small beneficial effect, but flatulence can be a problem;
- combining with pioglitazone or rosiglitazone.

Cautions
Sulphonylureas can encourage weight gain and should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting; metformin is considered the drug of choice in obese patients. Caution is needed in the elderly and in those with mild to moderate hepatic and renal impairment because of the hazard of hypoglycaemia. The short-acting tolbutamide may be used in renal impairment, as may gliclazide and gliclazide which are principally metabolised in the liver, but careful monitoring of blood-glucose concentration is essential; care is required to choose the smallest possible dose that produces adequate control of blood glucose.
GLIBENCLAMIDE

Mode of action
Increase pancreatic insulin secretion; may decrease insulin resistance.

Indications
Type 2 diabetes (includes combination with metformin)

Contraindications
Ketoacidosis
Type 1 diabetes

Specific considerations
Porphyria: risk of acute attacks.
Intercurrent illness (eg MI, coma, infection, trauma): monitor blood glucose and urine ketones; substitute insulin treatment if glycaemic control is inadequate.
Renal impairment: Increased risk of hypoglycaemia; avoid use.
Hepatic impairment: Increased risk of hypoglycaemia; avoid use.
Elderly: Increased risk of hypoglycaemia; avoid use.
Surgery: Substitute insulin treatment before surgery.
Pregnancy: Avoid use (replace with insulin); ADEC category C.
Breastfeeding: Avoid use.

Adverse effects
Hypoglycemia is the most frequent and serious adverse effect. Risk is increased by advanced age, renal or hepatic impairment and interacting drugs.
Common: weight gain, hypoglycaemia
Infrequent: nausea, diarrhoea, metallic taste, headache, rash
Rare: blood disorders (thrombocytopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia), allergic reaction, erythema multiforme, exfoliative dermatitis, photosensitivity, hepatotoxicity

Dosage
2.5–20 mg daily in 1–2 doses; up to 10 mg as single dose.

Counselling
Take tablets with food to minimise risk of low blood glucose (hypoglycaemia).
Drinking alcohol decreases your blood glucose. It can also mask warning symptoms of hypoglycaemia. Avoid binge drinking and have something to eat when you drink alcohol.
Make sure that you, and your friends and family, know how to recognise and treat hypoglycaemia; ask your doctor or diabetes educator if you are unsure.

Practice points
• start with low dose and increase at weekly intervals until control achieved
• increasing dosage at the upper limit of dose range may achieve little additional hypoglycaemic effect
• substitution with, or addition of, another sulfonylurea does not usually improve glucose control; instead, consider combined treatment with other classes of oral antidiabetic drugs or insulin, or monotherapy with insulin

Products
GLIBENCLAMIDE TABS 5 MG (EUGLUCON®, GLIBEMIDE®, GLIBESYN®, GLIBIL 5®, GLUCANA®, GLUCOMID®, GLUNIL®, MELIX®, RIVECLAMIDE®)

GLICLAZIDE

Mode of action
Same as Glibenclamide.

Indications
Type 2 diabetes (includes combination with metformin)

Contraindications
Ketoacidosis
Type 1 diabetes

Specific considerations
Same as Glibenclamide

Adverse effects
Hypoglycemia is the most frequent and serious adverse effect. Risk is increased by advanced age, renal or hepatic impairment and interacting drugs.

Common: weight gain, hypoglycaemia
Infrequent: nausea, diarrhoea, metallic taste, headache, rash
Rare: blood disorders (thrombocytopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia), allergic reaction, erythema multiforme, exfoliative dermatitis, photosensitivity, hepatotoxicity

**Dosage**
40–320 mg daily in 1–2 doses; up to 160 mg as single dose.
Controlled release formulation, initially 30 mg once daily; increase dose, according to response, by 30 mg once daily at not less than 2-week intervals; maximum daily dose 120 mg.

**Counselling**
Same as Glibenclamide

**Practice points**
- 30 mg of the controlled release formulation is equivalent to 80 mg of the conventional tablet
- start with low dose and increase at weekly intervals until control achieved
- increasing dosage at the upper limit of dose range may achieve little additional hypoglycaemic effect
- substitution with, or addition of, another sulfonylurea does not usually improve glucose control; instead, consider combined treatment with other classes of oral antidiabetic drugs or insulin, or monotherapy with insulin

**GLICLAZIDE TABS 30 MG (DIAMICRON MR®)**
**GLICLAZIDE TABS 80 MG (DIAMICRON®, DEBACRON®, DIAMID®, DUCLAZIDE®, MICROZIDE®)**

**GLIMEPIRIDE**
**Mode of action**
Same as Glibenclamide

**Indications**
Type 2 diabetes (includes combination with metformin)

**Contraindications**
Ketoacidosis
Type 1 diabetes

**Specific considerations**
**Adverse effects**
Same as Glibenclamide

**Dosage**
Initially, 1 mg once daily, adjusted according to response in 1 mg steps at 1–2 week intervals up to 4 mg once daily.

**Counselling**
Take tablets with food to minimise risk of low blood glucose (hypoglycaemia).
Drinking alcohol decreases your blood glucose. It can also mask warning symptoms of hypoglycaemia. Avoid binge drinking and have something to eat when you drink alcohol.
Make sure that you, and your friends and family, know how to recognise and treat hypoglycaemia; ask your doctor or diabetes educator if you are unsure.

**Practice points**
Same as Glibenclamide

**Products**
GLIMEPIRIDE TABS 2 MG (AMARYL®, GLEMAX®, GLORION®)

**06.01.02.02 Thiazolidinediones**

**PIOGLITAZONE**
**Mode of action**
Increase the sensitivity of peripheral tissues to insulin; decrease hepatic glucose output.

**Indications**
Type 2 diabetes, as monotherapy or with metformin, sulfonylureas or insulin.

**Contraindications**
Ketoacidosis
Type 1 diabetes
Heart failure NYHA class III and IV
Specific considerations
Mild-to-moderate heart failure (NYHA Class I or II): may worsen heart failure; start with a low dose and monitor carefully.
Treatment with insulin: increases risk of heart failure; use combination with caution.
Premenopausal anovulatory state, polycystic ovary syndrome: may restore fertility; consider contraception.
Intercurrent illness (eg MI, coma, infection, trauma): monitor blood glucose and urine ketones; substitute insulin treatment if glycaemic control is not adequate.
Hepatic impairment: Avoid use when transaminase levels are >2.5 times the upper limit of normal.
Surgery: Substitute insulin treatment before surgery.
Pregnancy: Avoid use; no human data; ADEC category B3.
Breastfeeding: Avoid use; no human data.
Adverse effects
Common: peripheral oedema, weight gain, headache, dizziness, arthralgia, decrease in haemoglobin and haematocrit.
Rare: elevated liver enzymes, hepatocellular injury, heart failure, pulmonary oedema
Dosage
15–30 mg once daily; may be increased to a maximum dose of 45 mg once daily after 6–8 weeks of treatment if effect is inadequate.
Wait several months before increasing dose in people with mild-to-moderate heart failure.
Counselling
Tell your doctor immediately if you have swollen feet or ankles, breathlessness, nausea, vomiting, abdominal pain, fatigue, loss of appetite or dark urine.
Practice points
- there are no data to justify use as monotherapy
- stop treatment if no effect after 6 months
- monitor liver enzymes at the start of treatment, then every 2 months for the first year and periodically thereafter
- check liver enzymes at the first symptoms suggestive of hepatic dysfunction
- stop treatment if ALT rises >3 times the upper limit of normal or if the patient has jaundice
- weight gain and pedal oedema are common adverse effects; assess risk of fluid retention before increasing dosage; consider stopping treatment if a diagnosis of heart failure is made
Products
PIOGLITAZONE TABS 15 MG (AS HCL) (ACTOS®)
ROSIGLITAZONE
Mode of action
Increase the sensitivity of peripheral tissues to insulin; decrease hepatic glucose output.
Indications
Type 2 diabetes, as monotherapy or with metformin, sulfonylureas, or insulin.
Contraindications
Ketoacidosis
Type 1 diabetes
Heart failure NYHA class III and IV
Specific considerations
Same as Pioglitazone
Adverse effects
Common: peripheral oedema, weight gain, headache, dizziness, arthralgia, decrease in haemoglobin and haematocrit, increase in total and HDL cholesterol (rosiglitazone)
Rare: elevated liver enzymes, hepatocellular injury, heart failure, pulmonary oedema
Dosage
Initially, 4 mg once daily; may be increased to 8 mg daily in 1 or 2 doses if effect is inadequate after 6–8 weeks of treatment.
Wait several months before increasing dose in people with mild-to-moderate heart failure.
Counselling
Tell your doctor immediately if you have swollen feet or ankles, breathlessness, nausea, vomiting, abdominal pain,
fatigue, loss of appetite or dark urine.

**Practice points**
Same as Pioglitazone

**Products**
ROSIGLITAZONE TABS 4 MG (AS MALEATE) (AVANDIA®)

### 06.01.02.03 Other Antidiabetics

**METFORMIN**

**Mode of action**
Reduces hepatic glucose production; increases peripheral utilisation of glucose.

**Indications**
Marketed: Type 2 diabetes as monotherapy or in combination with glibenclamide)
Accepted: With clomiphene for anovulatory infertility due to polycystic ovary syndrome (unresponsive to clomiphene alone) and body mass index >25, under specialist supervision

**Contraindications**
Moderate-to-severe heart failure
Respiratory failure
Severe infection or trauma
Dehydration
Alcohol misuse
Type 1 diabetes
Ketoacidosis
Conditions predisposing to lactic acidosis

**Specific considerations**
Renal impairment: Increases risk of lactic acidosis; reduce maximum dose in mild impairment, do not use when creatinine clearance is <30 mL/minute. Replace with insulin if possible.
Hepatic impairment: Avoid use; risk of lactic acidosis.
Surgery: Stop metformin 2 days before, during, and for 2 days after, surgery; monitor blood glucose concentrations; replace with insulin as required.
Elderly: use cautiously; avoid use in very old people, i.e. >85 years.
Avoid combination with glibenclamide (the fixed-dose combination is particularly unsuitable as dose titration is difficult).
Pregnancy: Usually replaced with insulin; some clinical use; ADEC category C.
Breastfeeding: Safe to use.

**Adverse effects**
Common: malabsorption of vitamin B12, nausea, vomiting, anorexia, diarrhoea
Infrequent: rash
Rare: acute hepatitis

**Lactic acidosis**
Rare, but often fatal. Caused by metformin accumulation when contraindications are overlooked, or in high risk situations (eg major illness, surgery). Early symptoms include anorexia, nausea, vomiting, abdominal pain, cramps, malaise and weight loss.

**Dosage**
Type 2 diabetes: 500 mg 1–3 times daily; may be increased up to 850 mg 2–3 times daily according to response.
Maximum daily dose 3 g.
Polycystic ovary syndrome: 500 mg 2–3 times daily as tolerated has been used, may be increased up to 2 g daily.
Renal impairment: A reduced maximum dose is suggested based on creatinine clearance:

- 60–90 mL/minute, 2 g daily
- 30–60 mL/minute, 1 g daily.

Combination with glibenclamide
Initially 1 tablet of 500 mg metformin with 2.5 mg glibenclamide daily with breakfast. Increase by 1 tablet every 2 weeks or longer according to response, to a maximum of 1 tablet of 500 mg metformin with 5 mg glibenclamide 3 times a day.
Elderly, the manufacturer suggests an initial dose of 250 mg metformin with 1.25 mg glibenclamide daily. Give with
breakfast and increase dose according to response as above.

**Counselling**

Take with meals to reduce stomach upset and the risk of low blood glucose (hypoglycaemia).

Tell your doctor immediately if you have loss of appetite, nausea, vomiting, abdominal pain, cramps, malaise, diarrhoea or weight loss.

Drinking alcohol decreases your blood glucose. It can also mask warning symptoms of hypoglycaemia and increase the risk of serious side effects. Limit your alcohol intake, avoid binge drinking and have something to eat when you drink alcohol.

Combination with glibenclamide

Ensure that you, and your friends and family, know how to recognise and treat hypoglycaemia; ask your doctor or diabetes educator if you are unsure.

**Practice points**

- slow onset of effect; control may take up to 2 weeks to establish
- monitor plasma creatinine before starting treatment and every 4–6 months
- increase dosage slowly to limit GI adverse effects; reduce or stop treatment if symptoms persist
- consider temporarily stopping treatment if illness occurs which may alter renal function (eg dehydration, shock, sepsis) or increase risk of tissue hypoxia and acidosis (eg MI, pulmonary embolism)
- use of iodinated contrast media increases risk of lactic acidosis; stop metformin 2 days before, during, and for 2 days after, administration of contrast media

**Combination with glibenclamide**

- monitor blood glucose when switching from standard tablets to fixed-dose combination because tablets are not bioequivalent
- do not use the previous doses of metformin and glibenclamide to start fixed-dose combination therapy

**Products**

METFORMIN TABS 850 MG (AS HCL) (DIABAMYL®, DIAMET®, DIPHAGE®, GLUCOPHAGE®, GLYMET®, METFORAL®)

**REPAGLINIDE**

**Mode of action**

Increases pancreatic insulin secretion.

**Indications**

Type 2 diabetes, as monotherapy or combined with metformin or insulin.

**Contraindications**

Ketoacidosis

Severe hepatic impairment, pregnancy and breast-feeding.

Type 1 diabetes

Treatment with gemfibrozil

**Specific considerations**

Intercurrent illness (eg MI, coma, infection, trauma): monitor blood glucose and urine ketones; substitute insulin treatment if glycaemic control is not adequate.

Renal impairment: Lower dosage required in severe impairment; titrate dose carefully in mild and moderate impairment.

Hepatic impairment: No data in severe impairment; titrate dose carefully in mild and moderate impairment.


Elderly: No data for people >75 years.

Children: Contraindicated in children <12 years.

Pregnancy: Avoid use; no data; ADEC category C.

Breastfeeding: Avoid use; no data.

**Adverse effects**

Hypoglycemia is the most frequent and serious adverse effect.

Common: nausea, vomiting, abdominal pain, diarrhoea, constipation,

Infrequent: rash, increase in liver enzymes

**Dosage**

Initially, 0.5 mg 3 times daily; increase every 1–2 weeks according to blood glucose control up to 4 mg 3 times daily.

Maximum dose 16 mg daily.

Changing from another oral antidiabetic drug
Initially, 1 mg 3 times daily.

**Counselling**
Take immediately before meals. Do not take a dose if you are skipping a meal. Drinking alcohol decreases your blood glucose. It can also mask warning symptoms of hypoglycaemia. Avoid binge drinking and have something to eat when you drink alcohol. Make sure that you, and your friends and family, know how to recognise and treat low blood glucose (hypoglycaemia); ask your doctor or diabetes educator if you are unsure.

**Products**

**REPAGLINIDE TABS 1 MG (NOVONORM®)**

**06.01.03 Treatment of Hypoglycaemia**

**HYPOGLYCAEMIA**
Hypoglycaemia can occur in people with diabetes receiving insulin, sulfonylureas or repaglinide. Mild hypoglycaemia will respond to oral administration of glucose or sucrose; give glucose (eg glucose tablets), not sucrose (cane sugar), to people treated with acarbose because of delayed absorption of sucrose. Treat severe hypoglycaemia in a person unable to take oral food or fluids with glucagon. If glucagon is not available or if there is no response in 10–15 minutes, give 20 mL of glucose 50% injection (into a secure IV cannula in an antecubital vein because of risk of superficial thrombophlebitis). In children, give glucose 10% injection (2 mL/kg over 3 minutes, followed by 0.1 mL/kg/minute until recovery). Recheck blood glucose as continued glucose boluses may render a young child hyperosmolar, with the risk of cerebral oedema. Prolonged treatment with glucose infusion may be required for hypoglycaemia due to a long acting sulfonylurea. Octreotide (SC 50 micrograms) may be used in patients with persisting hypoglycaemia despite glucose infusion. When the person has responded, give longer acting carbohydrates (eg a sandwich) to prevent recurrent hypoglycaemia.

**GLUCAGON**

**Mode of action**
Increases blood glucose concentration by activating hepatic glucose production; decreases GI motility.

**Indications**
Marketed: Hypoglycaemia induced by insulin or oral hypoglycaemic agents in people unable to take food or fluid orally. Diagnostic aid for GI radiological examination
Accepted: Adjunct in treatment of beta-blocker or calcium channel blocker overdose.

**Contraindications**
Insulinoma
Glucagonoma
Phaeochromocytoma

**Specific considerations**
Chronic hypoglycaemia, adrenal insufficiency, starvation: glucagon is ineffective.
Pregnancy: Safe to use; ADEC category B2.
Breastfeeding: Safe to use.

**Adverse effects**
Nausea, vomiting, hypokalaemia (large doses), allergic reactions

**Dosage**

**Hypoglycaemia**
Adult, child >5 years, 1 mg SC, IM or IV.
Child <5 years, 0.5 mg SC, IM or IV.

**Diagnostic aid**
IV/IM, 0.2–2 mg depending on radiological technique and route.

**Counselling**
Make sure that your friends and family know how to recognise low blood glucose (hypoglycaemia) and how to give glucagon injection; ask your doctor or diabetes educator if you are unsure.

**Practice points**
- person should respond to glucagon within 10–15 minutes; if there is no response, give IV glucose
- give oral carbohydrates when person has responded to prevent recurrent hypoglycaemia
06.02 DRUGS FOR THYROID DISORDERS

Thyroid and antithyroid drugs

06.02.01 Thyroid hormones

Thyroid hormones are used in hypothyroidism (myxoedema), and also in diffuse non-toxic goitre, Hashimoto's thyroiditis (lymphadenoid goitre), and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development.

Levothyroxine sodium (thyroxine sodium) is the treatment of choice for maintenance therapy. The initial dose should not exceed 100 micrograms daily, preferably before breakfast, or 25 to 50 micrograms in elderly patients or those with cardiac disease, increased by 25 to 50 micrograms at intervals of at least 4 weeks. The usual maintenance dose to relieve hypothyroidism is 100 to 200 micrograms daily which can be administered as a single dose.

In infants and children doses of thyroxine, for congenital hypothyroidism and juvenile myxoedema, should be titrated according to clinical response, growth assessment, and measurements of plasma thyroxine and thyroid-stimulating hormone.

LEVOTHYROXINE (THYROXINE SODIUM)

Also known as T₄

Indications

Hypothyroidism
Block-replace regimen in hyperthyroidism
Suppressive regimen in thyroid cancer and euthyroid goitre

Contraindications

Untreated hyperthyroidism, thyrotoxicosis

Specific considerations

Hypopituitarism and adrenal insufficiency: risk of acute adrenal crisis if used without glucocorticoid replacement.
Cardiovascular disorders: risk of worsening ischaemic symptoms; risk of arrhythmias.
Diabetes: may require adjustment of insulin or antidiabetic drug dosage when beginning treatment with thyroid hormones.
Elderly: require slower dosage adjustment; risk of cardiovascular adverse effects.
Children: thyroxine preferred; liothyronine rarely required. Try to avoid liothyronine because of preferential use of thyroxine by the developing brain.
Pregnancy: thyroxine is safe to use; increased dose (by about 25–40%) likely to be required; check thyroid function at least once each trimester; ADEC category A.

Try to avoid using liothyronine in pregnancy because of preferential use of thyroxine by the developing brain.
Breastfeeding: Safe to use.

Adverse effects

Usually associated with excessive dosage; correspond to symptoms of hyperthyroidism, eg tachycardia, arrhythmia, excitability, insomnia, flushing, sweating, diarrhoea and excessive weight loss.

Worsening ischaemic symptoms may occur in those with ischaemic heart disease, even at reduced doses.

Decreased bone density has been reported, particularly in over treated postmenopausal women and in suppressive regimens.

Infants treated with excessive doses may develop craniosynostosis and advancement of bone age.

Benign intracranial hypertension with headache, vomiting and papilloedema has been reported rarely in children in the first few weeks of treatment.

DOSAGE

Adult
Initially, 50–100 micrograms daily; increase by 25–50 micrograms daily every 3–4 weeks if necessary, according to TSH. Maintenance, 100–200 micrograms daily.

Child
<6 months, 8–10 micrograms/kg daily; up to 15 micrograms/kg daily in athyrosis.
7–12 months, 6–8 micrograms/kg daily.
1–5 years, 5–6 micrograms/kg daily.
6–12 years, 4–5 micrograms/kg daily (around 100 micrograms/m2 daily).
Elderly, ischaemic heart disease, severe hypothyroidism
Initially, 25–50 micrograms daily; increase daily dose by 25 micrograms every 6–8 weeks (or more frequently in severe cases) if necessary. Usual maintenance, 50–200 micrograms daily.

**Counselling**
Take thyroxine on an empty stomach, usually before breakfast.
Tell your doctor if symptoms of hyperthyroidism occur, eg palpitations, excitability, insomnia, flushing, sweating or weight loss.
Infants, the tablets can be easily dispersed in a small amount of milk or water.

**Practice points**
- if hyperthyroidism occurs, stop thyroxine for a week and restart at lower dosage

**Products**
LEVOTHYROXINE TABS 50 MCG (ELTROXIN®, EUTHYROX®, LEVOTHYROXINE®)
LEVOTHYROXINE TABS 100 MCG (ELTROXIN®, EUTHYROX®, LEVOTHYROXINE®)

**06.02.02 Antithyroid drugs**
Antithyroid drugs are used for hyperthyroidism either to prepare patients for thyroidectomy or for long-term management. Carbimazole is the most commonly used drug. Propylthiouracil may be used in patients who suffer sensitivity reactions to carbimazole as sensitivity is not necessarily displayed to both drugs. Both drugs act primarily by interfering with the synthesis of thyroid hormones.

**CSM warning (neutropenia and agranulocytosis)**
Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.
Patient should be asked to report symptoms and signs suggestive of infection, especially sore throat.
A white blood cell count should be performed if there is any clinical evidence of infection.
Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

**CARBIMAZOLE**

**Mode of action**
Block thyroid hormone synthesis; propylthiouracil also inhibits peripheral conversion of T₄ to T₃.

**Indications**
Graves' disease
Short term treatment before thyroid surgery, or before and after radioactive iodine treatment
Thyroid storm

**Contraindications**
Agranulocytosis with antithyroid drug

**Specific considerations**
Children: Seek specialist advice; neonatal thyrotoxicosis may occur as a rare complication of maternal Graves' disease.
Pregnancy: Use the lowest effective dosage; may induce fetal hypothyroidism; propylthiouracil preferred; do not use block-replace regimen; ADEC category C. Check TSH and free thyroid hormone every 6 weeks.
Carbimazole given during pregnancy has been linked to aplasia cutis, a rare congenital defect of the scalp, but the association has been questioned. Other increases in abnormalities may form part of a rare carbimazole embryopathy.
Breastfeeding: Propylthiouracil preferred because of lower secretion in breast milk; use the lowest effective dosage with appropriate monitoring of infant.

**Adverse effects**
Occur most often during the first 8 weeks of treatment. Itching and mild rashes may respond to antihistamines while continuing treatment; if a change in treatment is needed, the 2 drugs can often be interchanged without recurrence of adverse effects (unless agranulocytosis occurred, in which case seek specialist advice for future management).
Common: itching, rash, mild leucopenia, nausea, vomiting, gastric discomfort, headache, arthralgia
Rare: agranulocytosis, hypoprothrombinaemia and bleeding, myositis, hepatitis, vasculitis, lupus-like syndrome

**Dosage**

**Hyperthyroidism**

**Adult**
Initially, 20–40 mg daily (up to 60 mg daily in severe cases) in divided doses for 3–4 weeks.
Adjusted regimen, maintenance dose is usually 5–15 mg daily (but highly variable, range 2.5–40 mg daily) in single
or divided doses according to response. Block-replace regimen, continue initial dosage and add 100–150 micrograms thyroxine when T4 in normal range.

**Thyroid storm**
Adult, 60–80 mg daily, gradually reduced.

**Counselling**
Tell your doctor immediately if you develop a fever, mouth ulcers, sore throat or a rash.

**Products**
CARBIMAZOLE TABS 5 MG (CARBIMAZOLE®, NEOMERCAZOL®)

### 06.03 DRUGS AFFECTING BONE METABOLISM

#### OSTEOPOROSIS
Osteoporosis occurs most commonly in postmenopausal women and in those taking long-term oral corticosteroids (glucocorticosteroids). Other risk factors for osteoporosis include; low body weight, cigarette smoking, excess alcohol intake, lack of physical activity, family history of osteoporosis, and early menopause.

Those at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and any deficiency should be corrected by increasing dietary intake or taking supplements.

Elderly patients, especially those who are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and may benefit from supplements. Reversible secondary causes of osteoporosis such as hyperthyroidism, hyperparathyroidism, osteomalacia or hypogonadism should be excluded, in both men and women, before treatment for osteoporosis is initiated.

**Postmenopausal osteoporosis**
The bisphosphonates (alendronic acid, disodium etidronate, and risedronate) are effective for preventing postmenopausal osteoporosis. Hormone replacement therapy (HRT) is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. The CSM has advised that HRT should not be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years, but bone loss resumes (possibly at an accelerated rate) on stopping HRT. Calcitonin may be considered for those at high risk of osteoporosis for whom a bisphosphonate is unsuitable. Women of Afro-Caribbean origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.

Postmenopausal osteoporosis may be treated with a bisphosphonate. The bisphosphonates (such as alendronate, etidronate, and risedronate) decrease the risk of vertebral fracture; alendronate and risedronate have also been shown to reduce non-vertebral fractures. If bisphosphonates are unsuitable calcitriol or calcitonin may be considered.

Calcitonin [unlicensed indication] may also be useful for pain relief for up to 3 months after a vertebral fracture if other analgesics are ineffective.

**Corticosteroid-induced osteoporosis**
To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible. The risk of osteoporosis may be related to cumulative dose of corticosteroids; even intermittent courses can therefore increase the risk. The greatest rate of bone loss occurs during the first 6–12 months of corticosteroid use and so early steps to prevent the development of osteoporosis are important. Long-term use of high-dose inhaled corticosteroids may also contribute to corticosteroid-induced osteoporosis.

Patients taking (or who are likely to take) the equivalent of prednisolone 7.5 mg or more each day for 3 months or longer should be assessed and where necessary given prophylactic treatment; those aged over 65 years are at greater risk. Patients taking oral corticosteroids who have sustained a low-trauma fracture should receive treatment for osteoporosis.

**Rationale for drug use**
To prevent fractures and associated morbidity in people with low bone density or history of fracture.

**Before starting treatment**
Exclude other diseases that may cause bone fragility, eg metastatic cancer, multiple myeloma, osteomalacia. Consider specific causes, eg hypogonadism, hyperthyroidism, hyperparathyroidism, liver disease, malabsorption syndromes, Cushing's disease, especially in men or where bone density is >2.5 standard deviations (SD) below young mean value.

Evaluate risk factors and manage when possible:
- calcium intake, sunlight exposure, physical activity
- smoking, alcohol, medications, eg thyroxine, corticosteroids, some antiepileptic drugs, heparin
- age, gender, weight
- menstrual history, eg early menopause
- history of low-trauma fracture
- family history of low-trauma fracture.

Consider fall prevention, eg regular weight-bearing physical activity, balance training, medication management (reduce use of sedatives), improving poor vision, and home and environment modification.

Moderate activity levels, including walking, may lower hip fracture risk in postmenopausal women.

Evidence for efficacy of hip protectors is still conflicting; further data are required before recommending their use.

**When to start treatment**

Consider treatment in people with presence or history of osteoporotic fracture or when bone density is >2.5 SD below young mean value, especially if they have other risk factors for fracture.

**Drug choice**

**Calcium**

Adequate calcium intake should be part of routine management; total intake (including diet) should be 1200–1500 mg daily in postmenopausal women.

Supplementation may reduce bone loss in osteoporosis, particularly in late postmenopausal women with a low dietary calcium intake; less effective than other treatments when used as sole therapy.

**Vitamin D**

Cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂)

Increase bone density and reduce falls in older people.

In a study in institutionalised elderly women, vitamin D with calcium decreased risk of hip and vertebral fracture; however, results from other studies are conflicting. Vitamin D with calcium may not be effective for secondary prevention of low-trauma fractures in elderly people living in the community.

**Calcitriol**

Is the active form of vitamin D.

Reduces rate of bone density loss in postmenopausal osteoporosis; may reduce risk of vertebral fractures in women with a history of vertebral fracture; further efficacy data are required.

Monitor plasma calcium concentration regularly because of risk of hypercalcaemia and hypercalciuria.

**Bisphosphonates**

First line treatment of established postmenopausal osteoporosis. Alendronate and risedronate decrease risk of vertebral and non-vertebral fractures in postmenopausal women with a history of fracture.

Alendronate is also marketed for prevention of postmenopausal osteoporosis; however, it has not been shown to decrease risk of fractures in postmenopausal women with bone density <2.5 SD below young mean value.

Calcium and vitamin D supplements should be given with alendronate and risedronate if dietary intake is inadequate. They are poorly absorbed orally. There is a risk of oesophageal adverse effects with alendronate and a risk of osteomalacia with continuous use and high doses of etidronate (intermittent administration in cycles alternating with calcium is required).

Optimal duration of treatment with bisphosphonates is uncertain. There is limited evidence of additional protective effect after 5 years of treatment. Long term effects on bones due to skeletal retention are yet to be determined. Harmful effects such as delayed or absent fracture healing has been reported in long term users.

**Raloxifene**

Is a selective oestrogen receptor modulator.

Increases bone density in postmenopausal women (but less than oestrogen); decreases risk of vertebral fractures, but not risk of non-vertebral fractures in postmenopausal women with osteoporosis.

Increases risk of VTE similar to that with HRT.

Long term data are needed to confirm that raloxifene decreases risk of breast cancer and does not increase risk of endometrial cancer.

Improves lipid profile; lowers LDL cholesterol but no effect on HDL cholesterol and triglycerides.

Reduces cardiovascular morbidity in women at risk of cardiovascular disease.

Does not cause vaginal bleeding and breast discomfort but may aggravate hot flushes.

May be useful as second line treatment of postmenopausal osteoporosis in women at risk of breast cancer.

**Hormone replacement therapy**

The Women's Health Initiative study, a randomised trial in >16 000 postmenopausal women, confirmed benefit of HRT for prevention of hip and vertebral fractures. Risk of colorectal cancer was also slightly decreased. However, there was an increased risk of coronary heart disease, breast cancer, stroke and thromboembolism. The benefit of fracture reduction does not outweigh increased risk of cardiovascular disease and breast cancer.

In postmenopausal women who have had a hysterectomy use of unopposed oestrogens decreased risk of hip fracture
and increased risk of stroke and VTE, but did not appear to increase risk of coronary heart disease and breast cancer. **Teriparatide (human parathyroid hormone)**

Teriparatide increases bone density and decreases risk of vertebral fractures in postmenopausal women with established osteoporosis. There are fewer data in men with primary osteoporosis. Further data are needed to determine its place in treatment for osteoporosis. Currently it is used when other agents are unsuitable and there is a high risk of fracture.

Treatment is restricted to a total of 18 months (teriparatide caused osteosarcoma in animal studies).

**Strontium**

Decreases risk of vertebral fractures in postmenopausal women with established osteoporosis or risk factors for osteoporosis. A significant effect on hip fracture has not been shown.

No comparative data with bisphosphonates.

Long term safety data on consequences of skeletal uptake of strontium and possible muscular, thromboembolic and neurological adverse effects are required.

**Other drug treatment**

Calcitonins are not marketed for osteoporosis in Australia. There is limited evidence for long term prevention of fractures. Expense, adverse effects and difficulties with administration limit their use.

Androgens should not be used for osteoporosis because of lack of documented efficacy in preventing fractures and risk of serious adverse effects.

Fluoride should not be used for osteoporosis unless further studies show effective and safe regimens.

**Special cases**

Corticosteroid-induced osteoporosis

Measure bone density in people starting corticosteroids if they are likely to take these long term; look for corticosteroid-induced hypogonadism in men.

To minimise risks:

- use lowest effective dose of corticosteroids
- use topical or inhaled preparations instead of oral preparations when possible
- maintain adequate calcium intake, using calcium and vitamin D supplementation if necessary.

Most treatments used for corticosteroid-induced osteoporosis may prevent bone loss but further data are needed to assess their efficacy for preventing fractures.

Alendronate, etidronate and risedronate are marketed for prevention and treatment of corticosteroid-induced osteoporosis. There is some evidence that alendronate and risedronate prevent radiographic vertebral fractures.

Calcitriol is marketed for prevention of corticosteroid-induced osteoporosis; the risk of hypercalcaemia limits its use.

**Osteoporosis in men**

Secondary causes of osteoporosis are more common (eg hypogonadism, excess alcohol) and need specific treatment. Limited data are available about specific prevention and treatment of osteoporosis in men. Consider fall prevention and supplementation with calcium and vitamin D.

Alendronate and calcitriol are marketed for treatment of osteoporosis in men; alendronate may reduce risk of vertebral fractures; there is no evidence of benefit for calcitriol in men.

**PAGET’S DISEASE OF BONE**

**Rationale for drug use**

Relieve bone pain.

Prevent complications, eg bone deformities, pathological fractures, secondary osteoarthritis, neurological syndromes.

Preparation for orthopaedic surgery.

**When to start treatment**

Only 5% of people with Paget’s disease have symptoms and/or complications that require drug treatment.

Time to start treatment is influenced by:

- pain severity and persistence
- disease location and extent
- presence of complications
- age of person
- increase in biochemical markers of disease, eg plasma ALP, urinary hydroxyproline (may be normal in people with monostotic disease).

**Drug choice**

Bisphosphonates and calcitonins inhibit bone resorption, relieve bone pain and decrease biochemical markers.

**Bisphosphonates**
First line treatment.
Prolonged therapeutic effect (months to years).
Poor oral absorption; some may be given by intermittent IV infusion.
Risk of oesophageal adverse effects (which may be severe) with alendronate.
Etidronate can impair bone mineralisation, which limits dosage and treatment duration; avoid use in people with osteolytic lesions or fissure fractures of weight-bearing bones.
Long term effects on bones due to skeletal retention of the drugs remain to be determined.

**Salcatonin**
Rapid onset of analgesic effect (days to weeks).
Clinical response to treatment varies; limited biochemical effect (biochemical markers may not be reduced to the normal range).
Resistance to treatment may develop with rebound increase in biochemical markers during treatment; antibody-mediated resistance is rare despite frequent development of antibodies to salcatonin.
Short duration of remission after stopping treatment (some months); relapses tend to be increasingly resistant to repeated courses.
Adverse effects are common but usually improve with continuing drug use.
Available only as an injection.

**Practice points**
- monitor plasma ALP and urinary hydroxyproline concentrations before treatment and every 3 months
- ensure adequate calcium and vitamin D intake, especially during treatment with bisphosphonates, because of risk of osteomalacia
- initiate retreatment when symptoms recur or, in some circumstances, when biochemical markers increase by 20–25% above the minimum achieved after previous course

### 06.03.01 Bisphosphonates

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover. Bisphosphonates have an important role in the prophylaxis and treatment of osteoporosis and corticosteroid-induced osteoporosis; alendronic acid or risedronate sodium are considered the drugs of choice for these conditions, but disodium etidronate may be considered if these drugs are unsuitable or not tolerated.

Bisphosphonates are also used in the treatment of Paget's disease, hypercalcaemia of malignancy, and in bone metastases in breast cancer. Disodium etidronate can impair bone mineralisation when used continuously or in high doses (such as in the treatment of Paget’s disease).

**ALENDRONIC ACID**

**Mode of action**
Decrease bone resorption by inhibiting osteoclasts.

**Indications**
- Paget's disease of bone
- Prevention and treatment of osteoporosis (including postmenopausal and corticosteroid-induced)
- Hypercalcaemia of malignancy
- Osteolytic bone metastases from breast cancer or multiple myeloma

**Contraindications**
- Oesophageal disorders (active oesophagitis, oesophageal ulceration, stricture, achalasia)
- Inability to stand or sit upright for at least 30 minutes after drug administration
- Hypocalcaemia

**Specific considerations**
- Upper GI conditions (eg dysphagia, oesophageal disease, gastritis), concomitant use of NSAIDs: increase risk of oesophageal adverse effects.
- Renal impairment: Excreted unchanged mainly via the kidney. Limited data in patients with renal impairment. Deterioration of renal function has been reported; avoid use in severe impairment; reduce infusion rate during IV administration. Dose reduction may be required when creatinine clearance is <35 mL/minute.
- Pregnancy: No data available; avoid use ADEC category B3.
- Breastfeeding: No data available; avoid use.

**Adverse effects**
Common: nausea, vomiting, diarrhoea, musculoskeletal pain, headache
IV, fever, flu-like symptoms, injection site reaction, increased creatinine concentration, hypophosphataemia, hypomagnesaemia, hypocalcaemia, bone pain, myalgia, hypertension
Infrequent: oesophagitis, oesophageal erosions and ulcers (mainly with alendronate), gastritis, duodenitis, glossitis, iritis, uveitis, scleritis, rash
Rare: heart failure, renal impairment, osteonecrosis of the jaw, allergic reaction

**Dosage**
Paget’s disease
40 mg once daily for up to 6 months.
Treatment of postmenopausal osteoporosis and osteoporosis in men
10 mg once daily or 70 mg once a week.
Prevention of postmenopausal osteoporosis
5 mg once daily.
Treatment and prevention of corticosteroid-induced osteoporosis
5 mg once daily; 10 mg once daily for postmenopausal women not receiving oestrogen.

**Counselling**
Take in the morning with a full glass of water at least 30 minutes before food or drink. Remain upright during this time and until after you eat. Swallow whole; do not chew or suck on the tablet.
Do not take antacids, calcium, iron or mineral supplements within 30 minutes of alendronate as they may interfere with its absorption.
Stop tablets and see your doctor promptly if there is pain on swallowing, or new or worsening heartburn.

**Practice points**
- limited data available about multiple courses of alendronate in Paget’s disease
- for osteoporosis and Paget’s disease, ensure adequate intake of calcium and vitamin D; if necessary prescribe supplements (to be taken at a different time of day)
- complete dental procedures before treatment with IV bisphosphonates to minimise risk of osteonecrosis of the jaw

**Products**
ALENDRONIC ACID TABS 70 MG (ALENDOMAX®, FOSAMAX®)

**PAMIDRONIC ACID**
Disodium PAMIDRONATE

**Mode of action**
Same as Alendronic Acid.

**Indications**
Same as Alendronic Acid.

**Contraindications**
Hypocalcaemia

**Specific considerations**
Cardiac disease: risk of heart failure.
Predisposition to renal impairment (eg hypercalcaemia of malignancy, multiple myeloma): monitor renal function because of risk of acute renal failure.
Previous thyroid surgery: risk of hypocalcaemia.
Hepatic impairment: No data in severe impairment. Manufacturer suggests infusing at <20 mg/hour in mild-to-moderate impairment.
Renal impairment: Excreted unchanged mainly via the kidney. If creatinine clearance <30 mL/minute, avoid use unless life-threatening hypercalcaemia is present. In less severe impairment infuse at <20 mg/hour.
Pregnancy: No data available; avoid use ADEC category B3.
Breastfeeding: No data available; avoid use.

**Adverse effects**
Common: nausea, vomiting, diarrhoea, musculoskeletal pain, headache
IV, fever, flu-like symptoms, injection site reaction, increased creatinine concentration, hypophosphataemia, hypomagnesaemia, hypocalcaemia, bone pain, myalgia, hypertension
Infrequent: oesophagitis, oesophageal erosions and ulcers (mainly with alendronate), gastritis, duodenitis, glossitis, iritis, uveitis, scleritis, rash
Rare: heart failure, renal impairment, osteonecrosis of the jaw, allergic reaction
Dosage

Paget’s disease of bone
60 mg by slow IV infusion (15 mg/hour); optimal dosing regimen (interval between doses and total dose per treatment episode) adjusted individually according to response.

Hypercalcaemia of malignancy
Slow IV infusion (<60 mg/hour), dose adjusted according to initial plasma calcium concentration:
- <3.0 mmol/L, 30 mg
- 3.0–3.5 mmol/L, 30–60 mg
- 3.5–4.0 mmol/L, 60–90 mg
- >4.0 mmol/L, 90 mg.
Repeat dose every 2–3 weeks as necessary.

Bone metastases
Slow IV infusion (2 hours in breast cancer, 4 hours in multiple myeloma), 90 mg every 3–4 weeks.

Administration instructions
Dilute with sodium chloride 0.9% or glucose 5%.
Insert injection cannula carefully into a relatively large vein because of risk of local reactions.

Practice points
- monitor plasma concentrations of electrolytes, including calcium, magnesium and phosphate during treatment
- measure serum creatinine before each dose; if renal function deteriorates, withhold further dose until serum creatinine returns to within 10% of baseline value unless there is life-threatening hypercalcaemia
- restore and maintain adequate hydration with sodium chloride 0.9% in hypercalcaemia
- for osteoporosis and Paget’s disease, ensure adequate intake of calcium and vitamin D; if necessary prescribe supplements (to be taken at a different time of day)
- complete dental procedures before treatment with IV bisphosphonates to minimise risk of osteonecrosis of the jaw

Products

PAMIDRONIC ACID VIAL 30 MG/VIAL (AREDIA®, PAMIDRONATE®)

RISEDRONIC ACID
Risedronate Sodium

Mode of action
Same as Alendronic Acid.

Indications
Same as Alendronic Acid.

Contraindications
Hypocalcaemia
Inability to stand or sit upright for at least 30 minutes.

Specific considerations
History of oesophageal disorders, concomitant use of NSAIDs: increase risk of oesophageal adverse effects.
Renal impairment: Excreted unchanged mainly via the kidney Not recommended in moderate-to-severe impairment.
Pregnancy: No data available; avoid use; ADEC category B3.
Breastfeeding: No data available; avoid use.

Adverse effects
Common: nausea, vomiting, diarrhoea, musculoskeletal pain, headache.
IV, fever, flu-like symptoms, injection site reaction, increased creatinine concentration, hypophosphataemia, hypomagnesaemia, hypocalcaemia, bone pain, myalgia, hypertension
Infrequent: oesophagitis, oesophageal erosions and ulcers (mainly with alendronate), gastritis, duodenitis, glossitis, iritis, uveitis, scleritis, rash
Rare: heart failure, renal impairment, osteonecrosis of the jaw, allergic reaction

Dosage
Paget’s disease: 30 mg once daily for 2 months.
Postmenopausal osteoporosis: 5 mg once daily or 35 mg once a week.
Corticosteroid-induced osteoporosis: 5 mg once daily.

Counselling
Take in the morning with a full glass of water at least 30 minutes before food or drink. Remain upright during this
time and until after you eat. Swallow whole; do not chew or suck on the tablet. Do not take antacids, calcium, iron or mineral supplements within 2 hours of risendronate as they may interfere with its absorption. Stop tablets and see your doctor promptly if there is pain on swallowing, or new or worsening heartburn.

**Practice points**
- for osteoporosis and Paget's disease, ensure adequate intake of calcium and vitamin D; if necessary prescribe supplements (to be taken at a different time of day)
- complete dental procedures before treatment with IV bisphosphonates to minimise risk of osteonecrosis of the jaw

**Products**
**RISEDRONIC ACID TABS 5 MG (ACTONEL®)**

**ZOLEDRONIC ACID**

**Mode of action.**
Same as Alendronic Acid.

**Indications**
- Hypercalcaemia of malignancy
- Prevention of skeletal-related events in patients with advanced malignancies involving bone
- Paget's disease of bone
- Prevention and treatment of osteoporosis (including postmenopausal and corticosteroid-induced)

**Contraindications**
- Hypocalcaemia
- Pregnancy and breast feeding.
- Not recommended for children

**Specific considerations**
- Renal impairment: Excreted unchanged mainly via the kidney. No dosage adjustment required in mild impairment; avoid use in moderate-to-severe impairment.
- Reduce infusion rate during IV administration.
- Pregnancy: No data available; avoid use; ADEC category B3.
- Breastfeeding: No data available; avoid use.

**Adverse effects**
- Common: nausea, vomiting, diarrhoea, musculoskeletal pain, headache
- IV, fever, flu-like symptoms, injection site reaction, increased creatinine concentration, hypophosphataemia, hypomagnesaemia, hypocalcaemia, bone pain, myalgia, hypertension
- Infrequent: oesophagitis, oesophageal erosions and ulcers (mainly with alendronate), gastritis, duodenitis, glossitis, iritis, uveitis, scleritis, rash
- Rare: heart failure, renal impairment, osteonecrosis of the jaw, allergic reaction

**Dosage**
- Hypercalcaemia of malignancy
  - Initial treatment, 4 mg by IV infusion over 15 minutes.
  - Repeated treatment, 8 mg by IV infusion over 15 minutes at least 1 week after initial treatment in patients who are refractory to initial treatment or who subsequently relapse.
  - Prevention of skeletal-related events: 4 mg by IV infusion over no less than 15 minutes, repeated every 3–4 weeks.

**Administration instructions**
- Dilute with 100 mL sodium chloride 0.9% or glucose 5%.

**Practice points**
- restore and maintain adequate hydration with sodium chloride 0.9% in hypercalcaemia
- monitor calcium, phosphate and magnesium during treatment
- measure serum creatinine before each dose; if renal function deteriorates, withhold further dosing until serum creatinine returns to within 10% of baseline value unless there is life-threatening hypercalcaemia
- give supplemental calcium of 500 mg calcium and 10 micrograms (400 units) vitamin D daily to patients with advanced bone malignancies
- for osteoporosis and Paget's disease, ensure adequate intake of calcium and vitamin D; if necessary prescribe supplements (to be taken at different time of day)
- complete dental procedures before treatment with IV bisphosphonates to minimise risk of osteonecrosis of the jaw
06.03.02 Vitamin D substances

**ERGOCALCIFEROL**
Also known as vitamin D$_2$.

**Mode of action**
Regulate calcium homeostasis and bone metabolism. Increase intestinal absorption and renal reabsorption of calcium and phosphate. Promote bone mineralisation.

**Indications**
Prevention and treatment of vitamin D deficiency (osteomalacia in adults and rickets in children)
Hypocalcaemia in hypoparathyroidism, hypophosphataemic rickets, renal osteodystrophy, chronic renal dialysis
Treatment of osteoporosis
Prevention of corticosteroid-induced osteoporosis

**Contraindications**
Hypercalcaemia

**Specific considerations**
Renal impairment
Avoid use in severe impairment (inability to convert ergocalciferol to active form).
Hyperphosphataemia: risk of ectopic calcification; restrict dietary phosphate and/or give phosphate binders.
Pregnancy: Safe to use at physiological doses; seek specialist advice for use at pharmacological doses; fetal risk with untreated maternal vitamin D deficiency may be greater than risk of vitamin D-related hypercalcaemia in the infant.
Breastfeeding: Safe to use at physiological doses; risk of hypercalcaemia in the infant at pharmacological doses.

**Adverse effects**
Most adverse effects are due to effects of hypercalcaemia; increased risk with calcitriol because of its high potency.
Early symptoms of hypercalcaemia include nausea, vomiting, constipation, anorexia, apathy, headache, thirst, sweating and polyuria.
Renal and cardiovascular damage may occur because of ectopic calcification.

**Dosage**
Treatment of moderate-to-severe vitamin D deficiency
75–125 micrograms (3000–5000 international units) daily for 6–12 weeks then 25 micrograms (1000 international units) daily.
Prevention of vitamin D deficiency, osteoporosis: 10–20 micrograms (400–800 international units) daily.
Dose equivalence: 1 international unit is equivalent to 0.025 micrograms.

**Counselling**
Avoid taking other medications (including over-the-counter and health food preparations) that contain vitamin D.
Check with your pharmacist or doctor if you are unsure.

**Practice points**
- some multivitamin products contain 10 micrograms (400 international units)

**Products**
**ERGOCALCIFEROL (CALCIFEROL D2) AMPS 600,000 IU/AMP (NOT REGISTERED)**
**ERGOCALCIFEROL (CALCIFEROL D2) BOTTLE 2000 MCG/BOTTLE (NOT REGISTERED)**

06.03.03 Other Drugs Affecting Bone

**CALCITONIN**
Also known as salcatonin
Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homoeostasis. Calcitonin (salmon) (salcatonin, synthetic or recombinant salmon calcitonin) is used to lower the plasma-calcium concentration in some patients with hypercalcaemia (notably when associated with malignant disease). Calcitonin is licensed for treatment of Paget’s disease of bone. It can also be used in the prevention and treatment of postmenopausal osteoporosis

**Mode of action**
Calcitonin is a natural hormone involved in calcium regulation and bone metabolism. It inhibits bone resorption; increases urinary excretion of calcium and phosphate.
**Indications**
- Paget's disease of bone
- Hypercalcaemia

**Specific considerations**
- Renal impairment: May require dosage reduction.
- Children: Used in juvenile Paget's disease (hyperphosphatasia); dosing information limited, seek specialist advice.
- Pregnancy: Does not cross placenta; ADEC category B2.
- Breastfeeding: Safe to use.

**Adverse effects**
- Common: flushing, nausea, vomiting, dizziness
- Infrequent: inflammatory reaction at injection site
- Rare: tingling of hands, increased urinary frequency, allergic reactions, including rash and anaphylaxis

**Dosage**
- **Paget's disease**
  - SC/IM, 50–100 units daily for 3–6 months.
- **Hypercalcaemia**
  - 5–10 units/kg daily by slow IV infusion over at least 6 hours, or by slow IV injection in 2–4 divided doses.

**Administration instructions**
- Dilute with 500 mL sodium chloride 0.9% for IV infusion.

**Patient counselling**
- This medication can cause dizziness; avoid driving or operating machinery.

**Practice points**
- common adverse effects last for 1–2 hours after administration and usually improve with continuing drug use
- incidence of adverse effects may be reduced by giving SC rather than IM, administration at bedtime, giving once daily rather than twice daily, or use of an antiemetic
- antibodies may develop after prolonged treatment; while the development of resistance to calcitonins is not uncommon, antibody-mediated resistance to treatment is rare
- modest and transient effect seen in hypercalcaemia; tachyphylaxis typically develops over several days

**Products**
- CALCITONIN AMPS 100 IU/AMP 1 ML AMP (CALCO®, CALSYNAR®, MIACALCIC®)
- CALCITONIN NASAL SPRAY 200 IU/PUFF 2ML (14 PUFF) PER BOTTLE (MIACALCIC®, RAFACALCIN®)

**CALCIUM**

**Indications**
- Marketed: Calcium deficiency, Adjunctive treatment in osteoporosis, osteomalacia and rickets, Acute hypocalcaemia and hypocalcemia tetany, Hyperphosphataemia associated with renal failure (as phosphate binding agent), Severe hyperkalaemia not due to digoxin toxicity, Magnesium toxicity Hydrofluoric acid burns, Antacid
- Accepted: Acute verapamil and diltiazem poisoning.
  - Combination with cholecalciferol (vitamin D3), Osteoporosis

**Contraindications**
- Hypercalcaemia, Hypercalciuria, Digoxin toxicity

**Specific considerations**
- Hyperparathyroidism: use cautiously as a phosphate binder in renal impairment (monitor calcium concentration).
- Treatment with digoxin: combination may lead to arrhythmias; avoid using calcium injection solutions; monitor clinical effects, ECG and calcium concentrations if using oral calcium.
- Treatment with calcitriol: increases risk of hypercalcaemia; avoid combination unless dietary intake is clearly inadequate.
- Renal impairment: Monitor plasma calcium concentration; if necessary, reduce dosage or stop.
- Pregnancy: Safe to use.
- Breastfeeding: Safe to use.

**Adverse effects**
- Common: belching, flatulence, abdominal distension, constipation
Infrequent: hypercalcaemia, alkalosis, hypophosphataemia
Rare: renal calculi, milk-alkali syndrome
IV skin necrosis (extravasation), irritation.

**Milk-alkali syndrome**
Presentation acutely with headache, nausea, irritability and weakness or chronically with uraemia, alkalosis and hypercalcaemia; usually triggered by concomitant vomiting and/or sodium bicarbonate ingestion.

**Dosage**

**Calcium deficiency, adjunctive treatment in osteoporosis, osteomalacia, rickets**
Oral, adjust dose individually; the recommended daily intake of calcium for adults is 800 mg, 1100–1200 mg during pregnancy and lactation, and 1200–1500 mg in postmenopausal women.

**Acute hypocalcaemia:**
IV, 2.25–4.5 mmol of elemental calcium (10–20 mL calcium gluconate injection 10%) by slow injection; then adjust according to plasma calcium concentration.

**Hyperphosphataemia:**
Oral, 168–1200 mg elemental calcium (given as 420–3000 mg calcium carbonate) with each meal according to clinical response.

**Combination with cholecalciferol (vitamin D3):**
Oral, 1–2 tablets daily.

**Administration instructions**
Do not inject calcium solutions IM or SC as they are extremely irritant. Avoid extravasation during IV injection.

**Counselling**
Phosphate binder, if you skip a meal save your dose and take it when you next eat.

**Practice points**
- differences in formulation of calcium products (eg chewable tablet, effervescent tablet) may influence patient compliance

**Products**
CALCIUM CAPS 500 MG (AS DOPESILATE) (DOBESIL®, DOXIMUM®)

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**06.04 DRUGS FOR ADRENAL INSUFFICIENCY**

**Corticosteroids Therapy**
The adrenal cortex normally secretes hydrocortisone (cortisol) which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone.

In deficiency states, physiological replacement is best achieved with a combination of hydrocortisone and the mineralocorticoid fludrocortisone; hydrocortisone alone does not usually provide sufficient mineralocorticoid activity for complete replacement.

In Addison's disease or following adrenalectomy, hydrocortisone 20 to 30 mg daily by mouth is usually required. This is given in 2 doses, the larger in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion. The optimum daily dose is determined on the basis of clinical response. Glucocorticoid therapy is supplemented by fludrocortisone 50 to 300 micrograms daily.

In acute adrenocortical insufficiency, hydrocortisone is given intravenously (preferably as sodium succinate) in doses of 100 mg every 6 to 8 hours in sodium chloride intravenous infusion 0.9%.

In hypopituitarism glucocorticoids should be given as in adrenocortical insufficiency, but since the production of aldosterone is also regulated by the renin-angiotensin system a mineralocorticoid is not usually required. Additional replacement therapy with levothyroxine and sex hormones should be given as indicated by the pattern of hormone deficiency.

Corticosteroids regulate gene expression which results in:
- glucocorticoid effects, eg gluconeogenesis, proteolysis, lipolysis, suppression of inflammation and immune responses
- mineralocorticoid effects, eg hypertension, sodium and water retention, potassium loss.

Corticosteroids may have predominantly glucocorticoid effects (eg dexamethasone), mineralocorticoid effects (fludrocortisone), or a combination of both (eg hydrocortisone).

In comparing the relative potencies of corticosteroids in terms of their anti-inflammatory (glucocorticoid) effects it should be borne in mind that high glucocorticoid activity in itself is of no advantage unless it is accompanied by relatively low mineralocorticoid activity (see Disadvantages of Corticosteroids below). The mineralocorticoid
activity of fludrocortisone is so high that its anti-inflammatory activity is of no clinical relevance. The table below shows equivalent anti-inflammatory doses.

**EQUIVALENT ANTI-INFLAMMATORY DOSES OF CORTICOSTEROIDS**

This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action.

<table>
<thead>
<tr>
<th>Prednisolone 5 mg</th>
<th>Equivalent Anti-Inflammatory Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>≡ Betamethasone 750 micrograms</td>
<td></td>
</tr>
<tr>
<td>≡ Cortisone acetate 25 mg</td>
<td></td>
</tr>
<tr>
<td>≡ Dexamethasone 750 micrograms</td>
<td></td>
</tr>
<tr>
<td>≡ Hydrocortisone 20 mg</td>
<td></td>
</tr>
<tr>
<td>≡ Methylprednisolone 4 mg</td>
<td></td>
</tr>
<tr>
<td>≡ Triamcinolone 4 mg</td>
<td></td>
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</tbody>
</table>

The relatively high mineralocorticoid activity of cortisone and hydrocortisone, and the resulting fluid retention, make them unsuitable for disease suppression on a long-term basis. However, they can be used for adrenal replacement therapy; hydrocortisone is preferred because cortisone requires conversion in the liver to hydrocortisone. Hydrocortisone is used on a short-term basis by intravenous injection for the emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a useful topical corticosteroid for the management of inflammatory skin conditions because side-effects (both topical and systemic) are less marked; cortisone is not active topically.

Prednisolone has predominantly glucocorticoid activity and is the corticosteroid most commonly used by mouth for long-term disease suppression.

Betamethasone and dexamethasone have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high-dose therapy in conditions where fluid retention would be a disadvantage.

Betamethasone and dexamethasone also have a long duration of action and this, coupled with their lack of mineralocorticoid activity makes them particularly suitable for conditions which require suppression of corticotropin (corticotrophin) secretion (e.g. congenital adrenal hyperplasia). Some esters of betamethasone and of beclometasone (beclomethasone) exert a considerably more marked topical effect (e.g. on the skin or the lungs) than when given by mouth; use is made of this to obtain topical effects whilst minimising systemic side-effects (e.g. for skin applications and asthma inhalations).

**Disadvantages of corticosteroids**

Overdosage or prolonged use may exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid side-effects.

Mineralocorticoid side-effects include hypertension, sodium and water retention and potassium loss. They are most marked with fludrocortisone, but are significant with cortisone, hydrocortisone, corticotropin, and tetracosactide (tetracosactrin). Mineralocorticoid actions are negligible with the high potency glucocorticoids, betamethasone and dexamethasone, and occur only slightly with methylprednisolone, prednisolone, and triamcinolone.

Glucocorticoid side-effects include diabetes and osteoporosis, which is a danger, particularly in the elderly, as it may result in osteoporotic fractures for example of the hip or vertebrae; in addition high doses are associated with avascular necrosis of the femoral head. Mental disturbances may occur; a serious paranoid state or depression with risk of suicide may be induced, particularly in patients with a history of mental disorder. Euphoria is frequently observed. Muscle wasting (proximal myopathy) may also occur. Corticosteroid therapy is also weakly linked with peptic ulceration (the potential advantage of soluble or enteric-coated preparations to reduce the risk is speculative only).

High doses of corticosteroids may cause Cushing's syndrome, with moon face, striae, and acne; it is usually reversible on withdrawal of treatment, but this must always be gradually tapered to avoid symptoms of acute adrenal insufficiency.

In children, administration of corticosteroids may result in suppression of growth.
Adrenal Suppression
During prolonged therapy with corticosteroids, adrenal atrophy develops and may persist for years after stopping. Abrupt withdrawal after a prolonged period may lead to acute adrenal insufficiency, hypotension or death (see Withdrawal of Corticosteroids, below). Withdrawal may also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.
To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary re-introduction of corticosteroid treatment. Anaesthetists must therefore know whether a patient is taking or has been taking a corticosteroid, to avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period. A suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:
- Minor surgery under general anaesthesia: usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25–50 mg (usually the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery
- Moderate or major surgery: usual oral corticosteroid dose on the morning of surgery and hydrocortisone 25–50 mg intravenously at induction, followed by hydrocortisone 25–50 mg 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual pre-operative oral corticosteroid dose is recommenced on stopping hydrocortisone injections

Infections
Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. sepsis and tuberculosis may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated.
Chickenpox
Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunisation with varicella–zoster immunoglobulin is needed for exposed non-immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months; varicella–zoster immunoglobulin should preferably be given within 3 days of exposure and no later than 10 days. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased.
Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.
Measles
Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.
Use of Corticosteroids
Dosage of corticosteroids varies widely in different diseases and in different patients. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.
When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.
When potentially less harmful measures are ineffective corticosteroids are used topically for the treatment of inflammatory conditions of the skin. Corticosteroids should be avoided or used only under specialist supervision in psoriasis.
Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn's disease.
Use can be made of the mineralocorticoid activity of fludrocortisone to treat postural hypotension in autonomic neuropathy.
Although very high doses of corticosteroids have been given by intravenous injection in septic shock, a study of high-dose methylprednisolone sodium succinate did not demonstrate efficacy and, moreover, suggested a higher mortality in some subsets of patients given the high-dose corticosteroid therapy. However, there is evidence that
administration of lower doses of hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 micrograms daily by mouth) is of benefit in patients who have adrenocortical insufficiency as a consequence of septic shock.

Dexamethasone and betamethasone have little if any mineralocorticoid action and their long duration of action makes them particularly suitable for suppressing corticotropin secretion in congenital adrenal hyperplasia where the dose should be tailored to clinical response and by measurement of adrenal androgens and 17-hydroxyprogesterone. In common with all glucocorticoids their suppressive action on the hypothalamic-pituitary-adrenal axis is greatest and most prolonged when they are given at night. In most normal subjects a single dose of 1 mg of dexamethasone at night, is sufficient to inhibit corticotropin secretion for 24 hours. This is the basis of the 'overnight dexamethasone suppression test' for diagnosing Cushing's syndrome.

Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.

A corticosteroid may be used in the management of raised intracranial pressure or cerebral oedema that occurs as a result of malignancy; high doses of betamethasone or dexamethasone are generally used. However, a corticosteroid should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

In acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylactic shock, corticosteroids are indicated as an adjunct to emergency treatment with adrenaline (epinephrine). In such cases hydrocortisone (as sodium succinate) by intravenous injection in a dose of 100 to 300 mg may be required.

Corticosteroids are preferably used by inhalation in the management of asthma but systemic therapy in association with bronchodilators is required for the emergency treatment of severe acute asthma.

Corticosteroids may also be useful in conditions such as autoimmune hepatitis, rheumatoid arthritis and sarcoidosis; they may also lead to remissions of acquired haemolytic anaemia, and some cases of the nephrotic syndrome (particularly in children) and thrombocytopenic purpura.

Corticosteroids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis, and polyarteritis nodosa; the effects of the disease process may be suppressed and symptoms relieved, but the underlying condition is not cured, although it may ultimately remit. It is usual to begin therapy in these conditions at fairly high dose, such as 40 to 60 mg prednisolone daily, and then to reduce the dose to the lowest commensurate with disease control.

For other references to the use of corticosteroids see Prescribing in Palliative Care, (immunosuppression), (rheumatic diseases), (eye), (otitis externa), (allergic rhinitis), and (aphthous ulcers).

Pregnancy and breast-feeding

Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM has concluded:

- corticosteroids vary in their ability to cross the placenta; betamethasone and dexamethasone cross the placenta readily while 88% of prednisolone is inactivated as it crosses the placenta;
- there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip;
- when administration is prolonged or repeated during pregnancy, systemic corticosteroids increase the risk of intra-uterine growth restriction; there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome);
- any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important;
- prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant; infants should be monitored for adrenal suppression if the mothers are taking a higher dose.

Administration

Whenever possible local treatment with creams, intra-articular injections, inhalations, eye-drops, or enemas should be used in preference to systemic treatment. The suppressive action of a corticosteroid on cortisol secretion is least when it is given as a single dose in the morning. In an attempt to reduce pituitary-adrenal suppression further, the total dose for two days can sometimes be taken as a single dose on alternate days; alternate-day administration has not been very successful in the management of asthma. Pituitary-adrenal suppression can also be reduced by means of intermittent therapy with short courses. In some conditions it may be possible to reduce the dose of corticosteroid by adding a small dose of an immunosuppressive drug.
Withdrawal of corticosteroids
The CSM has recommended that gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have
- recently received repeated courses (particularly if taken for longer than 3 weeks)
- taken a short course within 1 year of stopping long-term therapy
- other possible causes of adrenal suppression
- received more than 40 mg daily prednisolone (or equivalent)
- been given repeat doses in the evening
- received more than 3 weeks’ treatment
Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have received treatment for 3 weeks or less and who are not included in the patient groups described above. During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 7.5 mg daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

DEXAMETHASONE
Indications
Where corticosteroids are indicated, eg cerebral oedema, prevention of neonatal respiratory distress syndrome, chemotherapy-induced nausea and vomiting, croup
Adrenal insufficiency
Immunosuppression in transplantation and autoimmune diseases
As an anti-inflammatory, eg in inflammatory bowel disease, asthma, allergy and skin conditions
Antepartum to prevent respiratory distress syndrome in premature infants
Adjuvant treatment of chemotherapy-induced nausea and vomiting
Contraindications
Except when used for adrenal insufficiency:
- Uncontrolled infection, Active peptic ulcer disease, Recent exposure to shingles, chickenpox or measles without prior immunity.
- Infective arthritis, Skin and soft tissue infections near joint (risk of introducing bacteria into joint), Prosthetic joint
Specific considerations
Except when used for adrenal insufficiency:
- Altered glucose tolerance: may increase insulin requirement or precipitate the need for insulin.
- Hypertension, heart failure: may be worsened by sodium and water retention (mineralocorticoid effect) and enhanced vascular reactivity; more likely to occur with cortisone or hydrocortisone (consider using alternative corticosteroid).
- Psychiatric disorders: may exacerbate psychosis and mood swings.
- Glaucoma: may increase intraocular pressure.
- Latent tuberculosis: may be reactivated; consider treatment with antitubercular drugs.
- Osteoporosis: may be exacerbated.
- Myasthenia gravis: increased muscle weakness may occur during treatment with corticosteroids; seek specialist advice.
- Clotting disorders or anticoagulant treatment: risk of joint haemorrhage with intra-articular injection, seek specialist advice.
- Surgery: Patients with hypothalamic–pituitary–adrenal (HPA) suppression or taking replacement doses of corticosteroids require corticosteroid protection against adrenal crisis during surgery and for 24–48 hours afterwards. Wound healing may be delayed by pharmacological doses of corticosteroids. Tight blood glucose control for 48 hours after surgery may reduce risk of wound infection. Dental procedures should be performed before immunosuppression or with antibacterial cover during immunosuppressive treatment. Children: Chronic use of corticosteroids may retard bone growth; follow growth and development carefully; catch-up growth may occur after corticosteroid withdrawal.
- Pregnancy: Safe to use; ADEC category A.
- Breastfeeding: Limited data available; consider using alternative corticosteroid, eg prednisolone.

Adverse effects
These adverse effects occur when corticosteroids are used for indications other than adrenal insufficiency. Incidence of adverse effects is related to dose, route of administration and duration of treatment. Systemic effects
may result from inhaled, intra-articular and topical treatment. Short courses of high dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses. Common: dyspepsia, increased susceptibility to infection (eg oral, vaginal and intertriginous candidiasis), masking of signs of infection, acne, oedema, hypertension, hypokalaemia, hyperglycaemia, osteoporosis, spontaneous fractures, increased appetite, delayed wound healing, skin atrophy, growth retardation in children, myopathy, muscle weakness and wasting (particularly symptomatic on drug withdrawal), fat redistribution (producing cushingoid appearance), amenorrhoea, psychosis, euphoria, depression, adrenal suppression, bruising
Infrequent: burning and tingling in perineal area (high dose IV treatment); vertebral compression fractures and aseptic necrosis of the talus, or femoral and humeral heads
Intra-articular injection: headache, flushing, rashes, acute post-injection flare reactions, injection site irritation, joint discomfort (brief), increased blood glucose concentration (temporary)
Rare: peptic ulceration with short courses of high doses, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions
Intra-articular injection: periarticular calcification (reversible), arthropathies, progressive cartilage damage, muscle wasting, skin and subcutaneous tissue atrophy, skin pigmentation changes, sterile abscess formation
Adrenal crisis
Acute cardiovascular collapse may occur when corticosteroids are abruptly stopped or if adrenal response is inadequate in periods of stress such as infection, trauma, surgery and blood loss.

**Dosage**

**Adult**
Cerebral oedema, IV 10 mg, then IM 4 mg every 6 hours; reduce dose over 5–7 days.
Prevention of neonatal respiratory distress syndrome, IM 6 mg every 12 hours for 4 doses (if delivery has not occurred).
Chemotherapy-induced nausea and vomiting, IV 8 mg, then oral 4 mg every 6 hours.
Bacterial meningitis, IV 10 mg every 6 hours for 4 days; start before or at the same time as antibacterials.

**Child**
Cerebral oedema, IV 1.5 mg/kg (maximum 10 mg), then 0.25 mg/kg every 4–6 hours; reduce dose over 5–7 days.
Croup, initially IV/IM 0.6 mg/kg, then oral for 2–3 days.
Chemotherapy-induced nausea and vomiting, IV/oral 0.2 mg/kg (maximum 8 mg), then 0.1 mg/kg (maximum 4 mg) every 6 hours.
Bacterial meningitis, IV 0.4 mg/kg every 12 hours for 2 days or 0.15 mg/kg every 6 hours for 4 days; start before or at the same time as antibacterials.
In adrenal insufficiency corticosteroids are used in doses which approximate physiological need (replacement doses); all other indications use doses that are supraphysiological (pharmacological doses).
Adjust dose according to response; higher doses are required for active disease than for maintenance treatment.

**Counselling**
Take the tablets or oral liquid with food to help reduce stomach upset.
Tell your doctor immediately if you have any signs of infection.
This medication may affect your mood, eg you may feel happy or sad; talk to your doctor if you have any concerns.
If you have been on this medication for more than 3 weeks the dose should be reduced gradually, not suddenly, when stopping treatment.
Tell all doctors, surgeons and dentists treating you that you are taking corticosteroids (or have taken them in the past). Consider wearing a Medic Alert® bracelet and carrying a card with the details of your treatment.

**Practice points**
- can also be given by intra-articular or soft tissue injection for local effect
- use of adjuvant IV dexamethasone (starting before or at the same time as IV antibacterials), reduces mortality and rate of complications of bacterial meningitis; when treating penicillin-resistant pneumococcal meningitis consider reduced CSF penetration of vancomycin due to corticosteroids
- corticosteroids are used for a wide range of conditions often without substantial evidence of their effectiveness

**When using pharmacological doses**
- measure blood glucose, weight, BP and electrolytes at baseline, then each week for the first month of treatment
- watch for signs/symptoms of infection; signs of infection may be masked
- avoid contact with faeces from a patient vaccinated with oral polio vaccine within the last 6 weeks as systemic infection may occur
consider treatment to suppress gastric acid when dose >15 mg daily of prednisolone or equivalent for >1 month
measure bone mineral density at baseline if likely to require repeat courses or chronic treatment
consider prevention of osteoporosis when beginning chronic treatment

**Stress and HPA suppression**
- use of pharmacological doses of corticosteroids may result in an inadequate adrenal response in periods of stress, eg infection, trauma, blood loss, because of HPA suppression
- degree of suppression depends on many factors and is particularly likely to occur with prolonged treatment (>3 weeks) and high doses
- adrenal response may be depressed for >1 year after corticosteroid-induced HPA suppression
- minimise suppression by giving corticosteroid doses in the morning or on alternate mornings
- during stress may need to give extra corticosteroid in addition to the usual dose, see Drugs for adrenal insufficiency

**Intra-articular injection**
- used for joints that fail to respond to systemic treatment
- use a sterile technique, aspirate fluid from joint if possible (do not proceed with the corticosteroid if you have any suspicion that there is infection)
- do not give >4 injections into any single joint over 1 year as there is a risk of developing progressive cartilage damage; seek specialist advice
- avoid further intra-articular injections if there is no response after 2 consecutive injections
- giving an intra-articular injection to a big toe affected by gout is generally not recommended because the procedure is very painful
- some practitioners use a mixture of local anaesthetic and corticosteroid to reduce discomfort following intra-articular injection
- instruct patients not to overuse the joint following intra-articular injection to avoid the risk of further joint deterioration and reduced beneficial effects

**Prevention of neonatal respiratory distress syndrome**
- give antenatal corticosteroid therapy to women 24–34 weeks gestation at risk of preterm delivery within 7 days
- betamethasone and dexamethasone are both effective in preventing neonatal respiratory distress syndrome
- repeat courses of corticosteroids should not be used routinely; evidence of a significant benefit is lacking; trials are ongoing.

**Products**
Dexamethasone Elixir 0.5 mg/5mL 100 ML Bottle (Decadron®)
Dexamethasone Tabs 0.5 mg (Decadron®, Dexamed®)

**Fludrocortisone**
Mineralocorticoid

**Indications**
Marketed: Mineralocorticoid replacement in adrenal insufficiency, with a glucocorticoid, Salt-losing congenital adrenal hyperplasia, with a glucocorticoid
Accepted: Orthostatic hypotension

**Specific considerations**
Heart failure: may be exacerbated by electrolyte changes and fluid retention; monitor and adjust fludrocortisone dosage carefully.
Low potassium concentrations: may be exacerbated by fludrocortisone-induced increase in potassium loss via the kidneys; monitor and treat accordingly (potassium supplementation may be needed).
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: No data available.

**Adverse effects**
When used as mineralocorticoid replacement, adverse effects usually indicate that the dose (and/or salt intake) is too high.
Common: sodium and water retention, oedema, hypokalaemia, hypertension
Rare: hypokalaemic alkalosis, heart failure
Dosage
Adrenal conditions: 50–100 micrograms once or twice daily, adjust as needed.
Orthostatic hypotension: Adult, initially 100 micrograms daily, increasing to 200 micrograms daily if necessary.

Counselling
Take this medicine with food to help reduce stomach upset.
Do not stop taking this medicine suddenly. Tell your doctor if you develop swelling of the feet or ankles, headaches or weakness.

Products
FLUDROCORTISONE TABS 100 MCG AS ACETATE (NOT REGISTERED)

HYDROCORTISONE
Glucocorticoid
Indications
Glucocorticoid replacement in adrenal insufficiency
Acute adrenal insufficiency
Dosage
Replacement therapy: Adult, child, oral, 8–20 mg/m2 daily (8–30 mg daily in adults) given in 2 doses with two-thirds of the dose in the morning and one-third in the evening; may be doubled or trebled and given more frequently (every 6–8 hours) during intercurrent illness.
Acute adrenal insufficiency: Adult, IV/IM, 100 mg repeated every 4–8 hours for 24 hours. Child, IV/IM, 25–50 mg/m2 every 4–8 hours for 24 hours.

Practice points
- patients and carers should know how to give IM hydrocortisone when oral intake is impossible and medical care is not available; this may be life saving

Products
HYDROCORTISONE TABS 10 MG (AS SUCCINATE) (NOT REGISTERED)
HYDROCORTISONE TABS 20 MG (AS SUCCINATE) (HYDROSONE®)
HYDROCORTISONE VIAL 100 MG/VIAL (AS SUCCINATE) (HYDROCORTISONE®, HYDROCORTISONE MEDO®, HYDROCORTISONE SOD SUCC®, SOLU-CORTEF®)

PREDNISOLONE (PREDNISONE)

Mode of action
Corticosteroids regulate gene expression which results in:
- glucocorticoid effects, eg gluconeogenesis, proteolysis, lipolysis, suppression of inflammation and immune responses
- mineralocorticoid effects, eg hypertension, sodium and water retention, potassium loss.

Indications
Same as Dexamethasone

Contraindications
Same as Dexamethasone

Specific considerations
Hepatic impairment: In severe impairment the conversion of prednisone to prednisolone may be diminished.
Breastfeeding: Safe to use; take dose immediately after a feed and wait 4 hours before the next feed. Doses up to 80 mg have been studied.

Adverse effects
Same as Dexamethasone

Dosage
Once condition has stabilised, reduce to the minimum required to maintain control of disorder.
Adult
Initial autoimmune or inflammatory disease control, 1–2 mg/kg once daily and taper according to response.
Rheumatoid arthritis, 5–10 mg once daily.
Acute liver transplant rejection, 200 mg once daily for 3 days.
Acute gout, 20–50 mg once daily for 3–5 days, then taper dose over 7–10 days.
In tertiary syphilis (with benzylpenicillin), 20 mg every 12 hours for 3 doses to reduce Jarisch–Hersheimer reaction.
Child: Autoimmune disease, initially 2 mg/kg once daily, reducing over 2 months to nil or the minimum required to sustain remission.
Nephrotic syndrome, 60 mg/m2 daily (maximum 80 mg) until remission, then reducing over 3–4 months to nil. Acute asthma, 1 mg/kg once daily for 3–5 days. Croup, 1 mg/kg every 12 hours for 1–2 doses. In adrenal insufficiency corticosteroids are used in doses which approximate physiological need (replacement doses); all other indications use doses that are supraphysiological (pharmacological doses). Adjust dose according to response; higher doses are required for active disease than for maintenance treatment.

**Counselling**
Same as Dexamethasone.

**Practice points**
- prednisone is converted to the pharmacologically active prednisolone in the liver
- Additional points: same as dexamethasone

**Products**
PREDNISOLONE TABS 5 MG (AS ACETATE) (CORTOPE 5®, PREDNISOLONE®)

**TETRACOSACTRIN**
Corticotrophin analogue

**Mode of action**
Stimulates synthesis and release of corticosteroids.

**Indications**
Diagnostic aid for adrenocortical insufficiency
Hypsarrhythmia and/or infantile spasms (long acting suspension, seek specialist advise)

**Specific considerations**
Allergic disorders: risk of allergic reactions.
Pregnancy: Avoid use; ADEC category D.
Breastfeeding: Inactive orally; safe to use.

**Adverse effects**
Allergic reactions including anaphylaxis, adrenal haemorrhage (isolated cases)

**Dosage**
Diagnosis of adrenal insufficiency, solution, IM 0.25 mg as a single dose.

**Practice points**
- failure to observe an adequate rise in plasma cortisol concentration (>500–650 nanomoles/L depending on the assay used) 30 minutes after administration of tetracosactrin (0.25 mg) may reflect adrenal insufficiency

**Products**
TETRACOSACTRIN AMPS 250 MCG/AMP (AS ACETATE) 1 ML AMP (NOT REGISTERED)

### 06.05 DRUGS FOR INFERTILITY

**INFERTILITY**
Treatment of infertility is highly specialised and depends on the cause.
Anovulatory infertility and polycystic ovary syndrome are commonly treated with clomiphene and occasionally with metformin or tamoxifen. Gonadotrophins (follicle stimulating hormones) may be used in women in whom clomiphene has been unsuccessful.
Women with hypopituitarism require FSH and LH. Multiple pregnancy is a major risk following ovulation induction with gonadotrophins. Risks of multiple pregnancies can be reduced by careful monitoring of follicle development by oestradiol measurement and ultrasound in a specialised unit.
Assisted reproduction techniques including in vitro fertilisation (IVF) and gamete intrafallopian transfer (GIFT) usually require down regulation with GnRH analogues (leuprolrelin or nafarelin) or with newer GnRH antagonists (ganirelix and cetrorelix) and artificial stimulation of ovarian follicle growth by gonadotrophins. HCG is commonly used in gonadotrophin-induced ovulation, IVF and GIFT to time release of eggs from the ovarian follicles and for luteal phase support. The combination of GnRH analogues, gonadotrophins and HCG is associated with a risk of serious ovarian hyperstimulation.
Progestrone is used for luteal phase support in assisted conception cycles when HCG is not recommended because of the risks of ovarian hyperstimulation. It is essential in assisted conception cycles when ovulation and natural progesterone production do not occur, eg treatment with donor oocytes; it is rarely indicated in natural conceptions. Bromocriptine or cabergoline may be used to normalise prolactin levels and induce ovulation in women with hyperprolactinaemia where surgical treatment is not indicated.
HCG and/or FSH may be used in infertile males with hypopituitarism.

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06.05.01 Gonadotrophines

**HUMAN CHORIONIC GONADOTROPHIN**
Also known as HCG.

**Mode of action**
Biological product; acts as LH.

**Indications**
Induction of ovulation in infertility and assisted reproduction techniques
Prepubertal cryptorchidism
Hypogonadotrophic hypogonadism

**Contraindications**
Ovarian cysts or enlargement not due to polycystic ovary syndrome
Genital bleeding of unknown origin
Ovarian, prostate, uterine or breast cancer
Hypothalamic or pituitary tumours
Fibroids incompatible with pregnancy

**Specific considerations**
Asthma, epilepsy, migraine, cardiovascular and renal disorders: risk of androgen-induced fluid retention.
Prepubertal boys: risk of premature closure of epiphyses.
Pregnancy: Contraindicated; ADEC category B3.
Breastfeeding: Avoid use.

**Adverse effects**
Common: local reaction at injection site, abdominal or pelvic pain, breast pain, nausea, headache, ovarian cyst, multiple pregnancy
Rare: allergic reaction
Ovarian hyperstimulation syndrome
Symptoms usually mild with slight ovarian enlargement and abdominal pain. Rarely, a severe, life-threatening syndrome occurs with large ovarian cysts prone to rupture, ascites, pleural effusion, thromboembolic disorders and death.

**Dosage**
Induction of ovulation
IM 5000–10 000 units as a single dose.
Cryptorchidism, hypogonadism
IM 500–4000 units 3 times a week.

**Practice points**
- use of these drugs is restricted to specialists; in assisted reproduction techniques, close monitoring of follicular development and oestrogen secretion is necessary for adjustment of dose and prevention of ovarian hyperstimulation syndrome

**Products**
CHORIONIC GONADOTROPHIN AMPS/VIAL 5000 IU/AMP (CHORIOMON®, CHORAGON®, GONACOR®, PREGNYL®)

**MENOTROPHIN LH+FSH (HUMAN MENOPAUSAL GONADOTROPHINS)**

**Uses and Administration**
Human menopausal gonadotrophins possess both follicle-stimulating hormone (FSH) activity and luteinising hormone (LH) activity at equal proportions. It is of pituitary origin obtained from the urine of postmenopausal urine. Human menopausal gonadotrophins are used in the treatment of male and female infertility due to hypogonadism. In anovulatory infertility unresponsive to clomifene, human menopausal gonadotrophins are administered to induce follicular maturation and are followed by treatment with chrorionic gonadotrophin to stimulate ovulation and corpus luteum formation. In women with polycystic ovary syndrome a gonadorelin analogue may be given beforehand to suppress pituitary gonadotrophin production.

The dosage and schedule of treatment for female infertility must be determined according to the needs of each patient; it is usual to monitor response by studying the patient's urinary oestrogen excretion or by ultrasonic visualisation of follicles, or both. Human menopausal gonadotrophins may be given daily by intramuscular or subcutaneous injection to provide a dose of 75 to 150 units of FSH and gradually adjusted if necessary until an
adequate response is achieved. Treatment is then stopped and followed after 1 or 2 days by single doses of chorionic gonadotrophin 5000 to 10 000 units. In menstruating patients treatment should be started within the first 7 days of the menstrual cycle. In the UK it has been suggested that the treatment course should be abandoned if no response is seen in 3 weeks although in the US the manufacturers recommend that an individual course should not exceed 12 days. This course may be repeated at least twice more if necessary. An alternative schedule is to give three equal doses by intramuscular or subcutaneous injection, each providing 225 to 375 units of FSH on alternate days followed by chorionic gonadotrophin one week after the first dose. In fertilisation procedures in vitro, or other assisted conception techniques, human menopausal gonadotrophins are used with chorionic gonadotrophin and sometimes also clomifene citrate or a gonadorelin analogue. Stimulation of follicular growth is produced by human menopausal gonadotrophins given by intramuscular or subcutaneous injection, in a dose providing 75 to 300 units of FSH daily, usually beginning on the 2nd or 3rd day of the menstrual cycle. An example of a combined regimen involves clomifene citrate 100 mg on days 2 to 6, with human menopausal gonadotrophins beginning on day 5 in a dose providing 150 to 225 units of FSH daily. Treatment is continued until an adequate response is obtained and the final injection of human menopausal gonadotrophins is followed 1 to 2 days later with up to 10 000 units of chorionic gonadotrophin. Oocyte retrieval is carried out about 32 to 36 hours later. In men with infertility due to hypogonadotrophic hypogonadism, spermatogenesis is stimulated with chorionic gonadotrophin and then human menopausal gonadotrophins are added in a dose of 75 or 150 units of FSH two or three times weekly by intramuscular or subcutaneous injection. Treatment should be continued for at least 3 or 4 months.

Adverse Effects
Human menopausal gonadotrophins may cause dose-related ovarian hyperstimulation varying from mild ovarian enlargement and abdominal discomfort to severe hyperstimulation with marked ovarian enlargement or cyst formation, acute abdominal pain, ascites, pleural effusion, hypovolaemia, shock and thromboembolic disorders. Rupture of ovarian cysts and intraperitoneal haemorrhage has occurred, usually after pelvic examination. Fatalities have been reported. Hypersensitivity reactions and local reactions at the injection site may occur. Nausea and vomiting, joint pains and fever have been reported; gynaecomastia, acne, and weight gain have occurred in men.

Precautions
Human menopausal gonadotrophins should not be given to pregnant patients. Use should be avoided in patients with abnormal genital bleeding, hormone sensitive malignancies such as those of the breast, uterus, prostate, ovaries or testes, or ovarian cysts or enlargement not caused by the polycystic ovary syndrome. Pituitary or hypothalamic lesions, adrenal or thyroid disorders, and hyperprolactinaemia should be treated appropriately to exclude them as causes of infertility before attempting therapy with human menopausal gonadotrophins. Patients who experience ovarian enlargement are at risk of rupture; pelvic examinations should be avoided or carried out with care and the recommendation has been made that sexual intercourse should be avoided while there is such a risk. There is a risk of multiple births.

Interactions
In women who show evidence of excessive ovarian stimulation while receiving human menopausal gonadotrophins the use of drugs with luteinising-hormone (LH) activity increases the risk of ovarian hyperstimulation syndrome.

Products
MENOTROPHIN (LH+FSH) (HUMAN MENOPAUSAL GONADOTROPHINS) AMPS 75+75 IU/AMP (MENOGON®, MENOPUR®, MERIONAL®)

06.05.02 Gonadotrophin-releasing hormone analogues
Gonadorelin when injected intravenously in normal subjects leads to a rapid rise in plasma concentrations of both luteinising hormone (LH) and follicle-stimulating hormone (FSH). It has not proved to be very helpful, however, in distinguishing hypothalamic from pituitary lesions. Gonadorelin analogues are indicated in endometriosis and infertility and in breast and prostate cancer.

Adverse Effects
Gonadorelin and its analogues are generally well tolerated but may cause gastrointestinal adverse effects, usually nausea and abdominal pain or discomfort. There may be headache or lightheadedness, and an increase in menstrual bleeding. Continued therapy with gonadorelin analogues results in paradoxical suppression of the pituitary gonadal axis; in premenopausal women this may produce menopausal symptoms, including vaginal dryness, hot flushes, and loss of libido. If sufficiently prolonged the suppression of circulating oestrogens may lead to osteoporosis. In men, hot flushes and sexual dysfunction have occurred. Breast swelling and tenderness in men have been reported infrequently with gonadorelin analogues. Other adverse effects reportedly associated with gonadorelin analogue...
therapy, and presumably related to changes in the hormonal milieu, include mood changes, nervousness, palpitations, acne and dry skin, alterations in liver function tests and blood lipids, decreased glucose tolerance, and changes in scalp and body hair. Ovarian hyperstimulation (as seen with chorionic gonadotrophin), although rare, has occurred in women given gonadorelin.

Reactions or pain may occur at the site of injection with rashes (local or generalised), thrombophlebitis, swelling, or pruritus. Hypersensitivity reactions, including bronchospasm and anaphylaxis, have been reported.

Other effects may be a consequence of the particular use of gonadorelin or its analogues. Tumour flare, due to an initial surge in testosterone concentrations, has been reported in the initial stages of treatment for cancer of the prostate and concomitant anti-androgen therapy may be given prophylactically. Flare may manifest as an increase in bone pain; occasionally there has been spinal cord compression, or a worsening of urinary-tract symptoms with haematuria and urinary obstruction. Acute degeneration of submucous fibroids with severe bleeding has been reported following use of leuprolin. An initial increase in signs and symptoms has also been reported in women with breast cancer receiving gonadorelin analogues; hypercalcaemia has occurred in those with metastatic disease.

**Precautions**

Gonadorelin or its analogues should not generally be used in patients with pituitary adenoma as haemorrhagic infarction (pituitary apoplexy) has sometimes occurred. It has also been recommended that patients with weight-related amenorrhoea should not receive these drugs until their weight is corrected. While it has been recommended by at least one manufacturer that gonadorelin should not be used in women with polycystic ovary disease or with endometriotic cysts, gonadorelin and its analogues have produced improvement in polycystic disease and in uterine fibroids, and gonadorelin analogues have been used with benefit in endometriosis. Gonadorelin or its analogues should be discontinued if the patient becomes pregnant. Contraceptive measures should be taken to protect against unwanted ovulation. Men at risk from tumour flare should be carefully monitored in the first month of therapy.

**Interactions**

Drugs affecting pituitary secretion of gonadotrophins may alter the response to gonadorelin or its analogues; other hormonal therapy and corticosteroids can affect the response. Spironolactone and levodopa can stimulate gonadotrophins while phenothiazines, dopamine antagonists, digoxin, and sex hormones can inhibit gonadotrophin secretion.

Gonadorelin, or more usually its analogues such as buserelin, goserelin, leuprolelin, nafarelin, and triptorelin (which are more potent and have a longer duration of action) are used in cryptorchidism, malignant neoplasms (especially of the prostate), and in delayed and precocious puberty.

Gonadorelin is sometimes used as the hydrochloride or acetate.

**Benign prostatic hyperplasia:** The gonadorelin analogues have been tried in the management of benign prostatic hyperplasia but are considered unsatisfactory for indefinite use.

**Cryptorchidism:** Whether gonadorelin or its analogues have a role in the management of cryptorchidism is a matter of debate; surgery remains the treatment with the best success rate, but hormonal therapy, with gonadorelin or chorionic gonadotrophin or both, is widely employed. Meta-analysis has suggested a success rate of about 20% overall, although this may be reduced when care is taken to exclude retractile testes.

**Premenstrual syndrome**

In women in whom other drug treatments for premenstrual syndrome are ineffective, use of a gonadorelin analogue, usually with HRT to prevent menopausal symptoms, may be considered. Short-term therapy (3 months) has been used to confirm the diagnosis of premenstrual syndrome, or to predict the response to bilateral oophorectomy when this is being considered.

**GONADORELIN (GNODORHINO–RELASE HORMONE;GNRH;LH-RH)**

**Mode of action**

GnRH stimulates synthesis of FSH and LH; continuous administration of GnRH analogues inhibits gonadotrophin production, suppressing ovarian and testicular steroidogenesis and inhibiting the growth of certain hormone-dependent tumours.

**Uses and Administration**

Gonadorelin is a synthetic form of hypothalamic gonadotrophin-releasing hormone. It stimulates the synthesis and release of follicle-stimulating hormone and, in particular, luteinising hormone in the anterior lobe of the pituitary. The secretion of endogenous gonadotrophin-releasing hormone is pulsatile and is controlled by several factors including circulating sex hormones. Gonadotrophic hormones (gonadotrophins), released from the pituitary gland in response to gonadorelin, stimulate secretion of sex hormones from the gonads. A single dose of gonadorelin or one of its analogues has the effect of increasing circulating sex hormones; continued administration leads to down-
regulation of gonadorelin-receptor synthesis in the pituitary and results in a paradoxical reduction in sex-hormone secretion.

Gonadorelin is used in the diagnosis of hypothalamic-pituitary-gonadal dysfunction. Assessment is usually based on the response to a dose of gonadorelin of 100 micrograms by intravenous or subcutaneous injection. In females, where possible, it should be given early in the follicular stage of the menstrual cycle.

Gonadorelin is also used in the treatment of amenorrhoea and infertility associated with hypogonadotrophic hypogonadism and multifollicular ovaries. Weight-related amenorrhoea should have been corrected by diet. Treatment in such conditions is based on an intermittent pulse pump providing 5 to 20 micrograms over one minute every 90 minutes for up to 6 months or until conception.

**Indications**

- Endometriosis
- Uterine fibroids
- Endometrial thinning before endometrial ablation
- Pituitary down regulation to prepare for controlled ovarian stimulation
- Advanced prostate cancer (stages C and D)
- Advanced breast cancer in premenopausal women
- Precocious puberty

**Contraindications**

- Pituitary tumour
- Undiagnosed vaginal bleeding

**Specific considerations**

- Urinary tract obstruction, metastatic vertebral lesions (prostatic cancer): risk of aggravation caused by tumour flare.
- Women at risk of decreased bone mass, eg weight-related amenorrhoea, immobilisation, corticosteroid use, family history of osteoporosis: risk of decreased bone mass.
- Polycystic ovarian disease: risk of cystic enlargement at the beginning of the treatment.
- Pregnancy: Contraindicated; ADEC category D.
- Breastfeeding: Contraindicated.

**Adverse effects**

- Common: hot flushes, sweating, amenorrhoea, withdrawal bleeding, sexual dysfunction, reduced libido, vaginal dryness, changes in breast size, breast tenderness, arthralgia, myalgia, peripheral oedema, dizziness, headache, nausea, vomiting, constipation, mood changes, injection site reaction, thrombophlebitis, decreased bone mass
- Infrequent: bronchospasm, rash
- Rare: paraesthesia, depression

**Flare**

A flare may develop during the first 2 weeks of treatment which may cause increased bone pain, and rarely ureteric obstruction or spinal cord compression, in patients with prostate cancer; and increased endometriotic symptoms and lesions in patients with endometriosis.

**Ovarian hyperstimulation syndrome**

Ovarian hyperstimulation syndrome may occur, mainly when GnRH analogues are used with FSH in assisted reproduction techniques. Symptoms are usually mild with slight ovarian enlargement and abdominal pain. Rarely, a severe and life-threatening syndrome can occur with large ovarian cysts prone to rupture, ascites, pleural effusion, thromboembolic disorders and death.

**Practice points**

- in non-cancer indications (eg endometriosis), courses >6 months and repeat courses are not recommended due to risk of decreased bone mass
- in women of child-bearing age, give first injection during menstruation or shortly afterwards to exclude pregnancy (except in some dosing schedules used for assisted reproduction); use non-hormonal methods of contraception to avoid unwanted pregnancy in the event of missed doses
- in infertility, monitor follicular development and oestrogen secretion to adjust dose and prevent ovarian hyperstimulation
- in controlled ovarian stimulation before in-vitro fertilisation, stop treatment at least 3 days before fertilised embryos are placed in the uterus

**Products**

GONADORELIN LH-RH AMPS 100 MCG/AMP (NOT REGISTERED)
**GOSERELIN**

**Mode of action**
Same as Gonadorelin

**Indications**
Marketed: Advanced prostate cancer (stages C and D)
Advanced breast cancer in premenopausal women
Adjuvant treatment in early breast cancer in pre- and peri-menopausal women
Endometriosis
Uterine fibroids
Endometrial thinning before endometrial ablation
Pituitary down regulation to prepare for controlled ovarian stimulation
Accepted: Precocious puberty, seek specialist advice
Advanced prostate cancer (stages C and D)

**Contraindications**
Pituitary tumour
Undiagnosed vaginal bleeding

**Specific considerations**
Same as Gonadorelin.

**Adverse effects**
Rare: transient changes in BP, hypercalcemia (in patients with metastatic breast cancer)
Others: Same as Gonadorelin.

**Dosage**
Endometrial thinning
SC, single 3.6 mg implant followed by surgery at 4 weeks, or two 3.6 mg implants inserted 4 weeks apart followed by surgery within 2–4 weeks of insertion of the second implant.
Endometriosis, uterine fibroids, assisted reproduction, breast cancer
SC, single 3.6 mg implant every 4 weeks (up to 6 months for endometriosis, for 3–6 months for uterine fibroids).
Prostate cancer:
SC, single 3.6 mg implant every 4 weeks, or single 10.8 mg implant every 12 weeks.

**Administration instructions**
Insert SC into the anterior abdominal wall.

**Practice points**
Same as Gonadorelin.

**Products**
GOSERELIN PFS 3.6 MG (AS ACETATE) (ZOLADEX®)
GOSERELIN PFS 10.8 MG (AS ACETATE) (ZOLADEX®)

**LEUPRORELIN**

**Mode of action**
Same as Gonadorelin and Goserlin

**Indications**
Marketed: Advanced prostate cancer (stages C and D)
Accepted: Precocious puberty, seek specialist advice
Pituitary down regulation to prepare for controlled ovarian stimulation, seek specialist advice
Endometriosis
Uterine fibroids
Endometrial thinning before endometrial ablation
Advanced breast cancer in premenopausal women

**Contraindications**
Same as Gonadorelin and Goserlin

**Specific considerations**
Same as Gonadorelin and Goserlin

**Adverse effects**
Same as Gonadorelin and Goserlin

**Dosage**
Prostate cancer: Immediate release injection, SC, 1 mg daily.
Depot injection: 7.5 mg every month, 22.5 mg every 3 months, 30 mg every 4 months or 45 mg every 6 months.

**Administration instructions**

Alternate injection sites.

**Practice points**

- consider starting treatment with daily leuprorelin injection rather than depot injection to facilitate treatment withdrawal if necessary; however, it is not known whether withdrawal will decrease flare reactions
- depot injections have different release rates, eg one-third of a 22.5 mg injection is not equivalent to the 7.5 mg injection
- dose for precocious puberty depends on clinical status

**Products**

- **LEUPRORELIN VIAL 3.75 MG/VIAL (AS ACETATE) (LUPRON®)**
- **LEUPRORELIN VIAL 22.5 MG/VIAL (AS ACETATE) (LUPRON®)**

**TRIPTORELIN**

**Uses and Administration**

Triptorelin is an analogue of gonadorelin with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in precocious puberty, and in the management of endometriosis, female infertility, and uterine fibroids. Triptorelin may be used as the base, acetate, diacetate, or embonate, although for preparations containing the acetate or diacetate it is not always obvious which has been used.

**Dosage**

Doses are usually given in terms of the base, and the following are each approximately equivalent to 1 mg of triptorelin:

- triptorelin acetate, 1.05 mg
- triptorelin diacetate, 1.09 mg
- triptorelin embonate, 1.30 mg

It is given as a daily subcutaneous injection, or as an intramuscular depot preparation lasting a month or longer. In the treatment of prostate cancer, a dose equivalent to triptorelin 3 or 3.75 mg is given intramuscularly as a depot preparation every 4 weeks; the first dose may be preceded by 100 micrograms daily for 7 days by subcutaneous injection. A longer-acting depot preparation that contains the equivalent of triptorelin 11.25 mg is given once every 12 to 13 weeks. An anti-androgen such as cyproterone acetate may be given for several days before beginning therapy with triptorelin and continued for about 3 weeks to avoid the risk of a disease flare.

Similar doses of the 3 or 3.75 mg depot preparations may be given for up to 6 months in the management of endometriosis or uterine fibroids, with treatment begun during the first 5 days of the menstrual cycle. In the management of female infertility doses of 100 micrograms subcutaneously daily, with gonadotrophins, have been recommended from the second day of the menstrual cycle for about 10 to 12 days.

In children with precocious puberty a dose equivalent to triptorelin 50 micrograms/kg from the 3-mg depot preparation may be given intramuscularly every 4 weeks. Alternatively, using the 3.75-mg preparation, doses of 1.875 mg for children weighing less than 20 kg, 2.5 mg for children of 20 to 30 kg, or 3.75 mg for children of more than 30 kg may be given; the first 3 doses should be given at 14-day intervals, with further doses given every 4 weeks.

**Delayed and precocious puberty.**

Gonadorelin analogues such as triptorelin1-4 are used in the management of central precocious puberty. They may also be effective in delayed puberty although they are most likely to be helpful where this is due to hypogonadism. Triptorelin has been used to differentiate gonadotrophin deficiency from constitutional delayed puberty.

**Disturbed behaviour.**

Combined therapy with triptorelin, which suppressed testosterone secretion by inhibiting the pituitary-gonadal axis, and supportive psychotherapy, has been tried in the treatment of men with paraphilias: a reduction in abnormal sexual thoughts and behaviours has been reported, although the study was uncontrolled.

**Endometriosis.**

Gonadorelin analogues are effective in the management of endometriosis, but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; ‘add-back’ therapy, with concomitant hormone replacement, can be used to prevent this.

**Fibroids.**

Gonadorelin analogues have been used as an alternative to surgery in the treatment of uterine fibroids, despite some concern that this may complicate the diagnosis of malignancy.
Infertility.
Gonadorelin analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both men and women.

Malignant neoplasms.
Triptorelin, like other gonadorelin analogues, may be used in the production of androgen blockade in patients with prostate cancer.

Porphyria.
Triptorelin has been used successfully to suppress premenstrual exacerbations of acute intermittent porphyria, in doses of 3.75 mg by intramuscular depot injection given monthly.1,2 To reduce the risk of osteoporosis, 'add-back' therapy with topical oestrogen and oral calcium was used in one case,1 and tibolone in another.

Pharmacokinetics
Triptorelin is rapidly absorbed following subcutaneous injection, with peak plasma concentrations achieved about 40 minutes after a dose. The biological half-life has been stated to be about 7.5 hours, although longer half-lives have been reported in patients with prostate cancer, and shorter half-lives in some groups of healthy subjects.

Adverse Effects and Precautions
As for Gonadorelin.
Effects of Buserelin Acetate

Products
TRIPTORELIN VIAL 3.75 MG/VIAL (AS ACETATE) (DECAPEPTYL®, GONAPEPTYL®)
TRIPTORELIN VIAL 11.25 MG/VIAL (AS ACETATE) (DECAPEPTYL®)

06.05.03 Treatments of anovulatory infertility

ANTI-OESTROGENS
The anti-oestrogens clomifene (clomiphene) and tamoxifen are used in the treatment of female infertility due to oligomenorrhoea or secondary amenorrhoea (e.g. associated with polycystic ovarian disease). They induce gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; chorionic gonadotrophin is sometimes used as an adjunct. Patients should be warned that there is a risk of multiple pregnancy (rarely more than twins).

CLOMIPHENE CITRATE
Mode of action
Competitively antagonises oestrogen receptors in the hypothalamus. This interferes with normal negative feedback mechanisms and increases the release of pituitary gonadotrophins, especially LH, inducing ovulation.

Indications
Anovulatory infertility

Contraindications
Abnormal uterine bleeding (determine cause before starting treatment)
Endometrial carcinoma

Specific considerations
Ovarian cysts: may enlarge during treatment.
Hepatic impairment: Avoid use in severe impairment.
Pregnancy: Avoid use; ADEC category B3.
Breastfeeding: May reduce milk supply.

Adverse effects
Common: hot flushes, abdominal discomfort, visual blurring, reversible ovarian enlargement and cyst formation
Infrequent: abnormal uterine bleeding, nausea, vomiting
Rare: hair loss (reversible), ovarian hyperstimulation syndrome (see Practice points)

Dosage
50–100 mg daily for days 2–6 of the menstrual cycle. Specialist guidance necessary.

Counselling
Stop taking this medicine and tell your doctor if your vision becomes blurred; avoid driving or using machinery if you are affected.

Practice points
• check liver function before starting treatment
clomiphene is used for polycystic ovary syndrome, but there is a significantly increased risk of multiple pregnancy if it is successful
ovarian hyperstimulation syndrome may occur in women with polycystic ovary syndrome, especially if pregnancy occurs in the cycle where clomiphene is given; pregnancy rates are poor in severe polycystic ovary syndrome

**Products**
CLOMIFENE TABS 50 MG (AS CITRATE) (CLOMID®, CLOMIFERT®, CLOMOVAL®, DUINUM®, FERTILINE®, INFANTRIL®, OVAMIT®, PROLIFEN®)

## 06.06 DRUGS FOR OTHER ENDOCRINE DISORDERS
### 06.06.01 Growth hormone

Growth hormone is used to treat deficiency of the hormone in children and in adults (see NICE guidance below). In children it is used in Prader-Willi syndrome, Turner’s syndrome and in chronic renal insufficiency; growth hormone has also recently been licensed for use in short children considered small for gestational age at birth. Growth hormone of human origin (HGH; somatotrophin) has been replaced by a growth hormone of human sequence, somatropin, produced using recombinant DNA technology.

**NICE guidance (somatropin in children with growth failure)**
NICE has recommended (May 2002) treatment with somatropin for children with:
- proven growth-hormone deficiency;
- Turner’s syndrome;
- Prader-Willi syndrome;
- chronic renal insufficiency before puberty.

Treatment should be initiated and monitored by a paediatrician with expertise in managing growth-hormone disorders; treatment can be continued under a shared-care protocol by a general practitioner.

Treatment should be discontinued if the response is poor (i.e. an increase in growth velocity of less than 50% from baseline) in the first year of therapy.

In children with chronic renal insufficiency, treatment should be stopped after renal transplantation and not restarted for at least a year

**NICE guidance (somatropin for adults with growth hormone deficiency)**
NICE has recommended (August 2003) somatropin in adults only if the following 3 criteria are fulfilled:
- Severe growth hormone deficiency, established by an appropriate method,
- Impaired quality of life, measured by means of a specific questionnaire,
- Already receiving treatment for another pituitary hormone deficiency.

Somatropin treatment should be discontinued if the quality of life has not improved sufficiently by 9 months.

Severe growth hormone deficiency developing after linear growth is complete but before the age of 25 years should be treated with growth hormone; treatment should continue until adult peak bone mass has been achieved. Treatment for adult-onset growth hormone deficiency should be stopped only when the patient and the patient’s physician consider it appropriate.

Treatment with somatropin should be initiated and managed by a physician with expertise in growth hormone disorders; maintenance treatment can be prescribed in the community under a shared-care protocol.

**SOMATROPIN**

Synthetic human growth hormone

**Mode of action**
Promotes growth of skeletal, muscular and other tissues; stimulates protein anabolism and influences fat and mineral metabolism.

**Indications**
Short stature in children due to growth hormone deficiency, Turner’s syndrome, chronic renal insufficiency, Prader–Willi syndrome or intrauterine growth retardation without spontaneous catch up by age 2
To correct neonatal hypoglycaemia due to growth hormone deficiency
Growth hormone deficiency and precocious puberty, irrespective of height and growth velocity
Growth hormone deficiency in adults

**Contraindications**
Active intracranial tumour or malignancy
Children with closed epiphyses
Acute critical illness due to trauma, abdominal or open heart surgery, or respiratory failure
With Prader–Willi syndrome, severe obesity, history of respiratory impairment, sleep apnoea, or unidentified respiratory infection
Allergy to somatropin or excipients

Specific considerations

Diabetes: risk of hyperglycaemia; adjust dosage of insulin or oral antidiabetic drugs.
Hypothyroidism: can reduce response to soma-tropin, monitor thyroid function and give thyroxine if necessary.
Reduced thyroid stimulating hormone reserve (eg multiple pituitary hormone deficiencies): somatropin treatment may lead to secondary hypothyroidism.
Previous intracranial tumour: monitor for progression and recurrence.
Children post-renal transplant: seek specialist advice.
Pregnancy: Avoid use; ADEC category B2.
Breastfeeding: Avoid use.

Adverse effects

Common: local skin reaction (at injection site), peripheral oedema, arthralgia, growing pains in shins, carpal tunnel syndrome (in adults), paraesthesia (in adults)
Infrequent: hyperglycaemia, lipodystrophy (at injection site), exacerbation of scoliosis, increase in number and size of naevi, acral enlargement, excessive loss of central body fat, slipped capital epiphysis
Rare: papilloedema, benign intracranial hypertension, systemic allergic reaction

Dosage

1 mg somatropin is equivalent to 3 units. Individualise dosage according to response.
Adult: Initially, 40 micrograms/kg each week, divided into daily SC injections; up to 80 micrograms/kg each week.
Child: 4.5–7.5 mg/m²/week, divided into daily SC injections. Up to 9.5 mg/m²/week in Turner’s syndrome and chronic renal insufficiency.

Administration instructions

Rotate injection site to prevent lipodystrophy.

Practice points

- reports of Creutzfeldt–Jakob disease in people who received growth hormone extracted from human pituitary glands resulted in withdrawal of pituitary-derived preparations; because of the long incubation period new cases of infection may still be reported
- gradual increase in dosage (eg starting at half or one-third of the recommended dosage) seems to minimise risk of adverse effects
- watch for limping as this may indicate development of a slipped capital epiphysis
- check for papilloedema if severe or recurrent headache, visual problems, nausea or vomiting occur
- all products are now synthesised by recombinant DNA technology; however, synthesis and purification processes are different for each brand; do not change formulation during treatment because it may increase antibody response and complicate long term follow-up of drug safety
- somatropin antibodies may develop in some people; they do not usually affect somatropin activity; however, testing for antibodies can be performed in people who fail to respond to treatment

Products

SOMATROPIN VIAL IU/ML (DIFFERENT CONCENTRATION 4 I.U, 5 MG/1.5, 10MG/1.5ML, 5.3 MG (GENOTROPIN®, GROWTROPIN®, HUMATROPE®, NORDITROPIN®, NORDILET®, SAIZEN®))

06.06.02 Somatostatin analogues

Octreotide and lanreotide are analogues of the hypothalamic release-inhibiting hormone somatostatin. They are indicated for the relief of symptoms associated with neuroendocrine (particularly carcinoid) tumours and acromegaly. Additionally, lanreotide is licensed for the treatment of thyroid tumours and octreotide is also licensed for the prevention of complications following pancreatic surgery; octreotide may also be valuable in reducing vomiting in palliative care and in stopping variceal bleeding (unlicensed indication).

Cautions

Growth hormone-secreting pituitary tumours can expand causing serious complications; during treatment with somatostatin analogues patients should be monitored for signs of tumour expansion (e.g. visual field defects). Ultrasound examination of the gallbladder is recommended before treatment and at intervals of 6–12 months during treatment (avoid abrupt withdrawal of short-acting octreotide: see Side-effects below). In insulinoma an increase in
the depth and duration of hypoglycaemia may occur (observe patients when initiating treatment and changing doses); in diabetes mellitus, insulin or oral antidiabetic requirements may be reduced.

LANREOTIDE

Mode of action
Inhibit release of growth hormone and of various peptides of the gastroenteropancreatic endocrine system; have a more prolonged duration of action than somatostatin (natural growth hormone inhibiting peptide).

Indications
Acromegaly where surgery, radiotherapy or dopamine agonist treatment have failed to control disease
Relief of symptoms associated with carcinoid tumours

Specific considerations
Insulinoma: possible increase in severity and duration of hypoglycaemia.
Diabetes: variable effect on blood glucose; adjust dose of insulin and oral antidiabetic drugs.
Gastroenteropancreatic endocrine tumours: occasional sudden escape from symptomatic control with rapid recurrence of severe symptoms.
Pregnancy: Avoid use; may produce fetal growth retardation, probably due to suppression of growth hormone; ADEC category C.
Breastfeeding: Avoid use.

Adverse effects
Common: abdominal pain, flatulence, nausea, vomiting, diarrhoea, gallstones, fatigue, hyperglycaemia, hypoglycaemia, hair loss, transient local reaction at injection site
Rare: hypothyroidism, pancreatitis, hepatic dysfunction

Dosage
Acromegaly: IM, initially 30 mg every 2 weeks. Maintenance, adjust dosing intervals according to response.
No previous treatment with a somatostatin analogue, initially SC 60 mg once every 28 days. Maintenance, adjust dose strength according to response.
Previous treatment with Somatuline
- every 14 days, initial dose SC 60 mg every 28 days
- every 10 days, initial dose SC 90 mg every 28 days
- every 7 days, initial dose SC 120 mg every 28 days.
Maintenance, adjust dose strength according to response.
Carcinoid tumours: Initially, SC 60–120 mg every 28 days, then adjust dose according to response.

Administration instructions
Rotate injection sites, should be given in the upper outer quadrant of the buttock.

Practice points
- monitor thyroid function during long term treatment
- ultrasound of the gall bladder before, and every 6–12 months during, treatment is recommended by the manufacturers

Products
LANREOTIDE VIAL 30 MG/VIAL (AS ACETATE) (SOMATULINE®)

OCTREOTIDE

Mode of action
Same as Lanreotide

Indications
Marketed: Acromegaly where surgery or radiotherapy are contraindicated or have failed to control disease, or until radiotherapy becomes fully effective
Relief of symptoms associated with gastroenteropancreatic tumours, eg carcinoid tumours, VIPomas
Prevention of complications following pancreatic surgery (SC octreotide only)
Accepted: Glucagonomas (seek specialist advice)

Specific considerations
Same as Lanreotide

Adverse effects
Common: abdominal pain, flatulence, nausea, vomiting, diarrhoea, gallstones, fatigue, hyperglycaemia, hypoglycaemia, hair loss, transient local reaction at injection site
Rare: hypothyroidism, pancreatitis, hepatic dysfunction
Dosage

Acromegaly
SC, initially, 50–100 micrograms every 8–12 hours. Maintenance, 200–300 micrograms daily.
IM, initially, 20 mg every 4 weeks for 3 months. Start the day after the last dose of SC octreotide. Maintenance, adjust dosage according to clinical and biological response.

Gastroenteropancreatic tumours
SC, initially, 50 micrograms once or twice daily. Maintenance, up to 200 micrograms 3 times daily. Higher doses may be required.
IM, initially, 20 mg every 4 weeks for 3 months. Continue octreotide SC for 2 weeks after first dose of long acting IM octreotide. Maintenance, adjust dosage according to clinical and biological response.

Pancreatic surgery:
SC, 100 micrograms 3 times daily for 7 days from the day of operation.

Administration instructions
Rotate injection sites. Give long acting octreotide by deep intragluteal injection only; avoid deltoid injection because of significant discomfort.

Practice points
- GI adverse effects may occur at start of treatment and usually subside spontaneously in 10–14 days; they may be reduced by injecting between meals or at bedtime
- avoid abrupt withdrawal of SC octreotide; risk of biliary colic and pancreatitis
- monitor thyroid function during long term treatment
- ultrasound of the gall bladder before, and every 6–12 months during, treatment is recommended by the manufacturers

Products
- OCTREOTIDE AMPS 0.1 MG/AMP  1 ML AMP (SANDOSTATIN®)
- OCTREOTIDE AMPS 0.5 MG/AMP  1 ML AMP (NOT REGISTERED)
- OCTREOTIDE AMPS 10 MG/PFS  1 ML PFS (SANDOSTATIN®)
- OCTREOTIDE AMPS 20 MG/PFS  1 ML PFS (SANDOSTATIN®)

06.06.03 Antidiuretic hormone analogues and antagonists

DESMOPRESSIN
Also known as DDAVP

Mode of action
Increases tubular reabsorption of water; increases factor VIII and von Willebrand's factor coagulation activity.

Indications
Diagnostic aid for differential diagnosis of polyuria
Pituitary diabetes insipidus, Nocturnal enuresis, Control of bleeding in patients with mild or moderate haemophilia and type I von Willebrand's disease (seek specialist advice), Control of bleeding in surgery in people with certain platelet disorders (seek specialist advice)

Contraindications
Heart failure, Type IIb von Willebrand's disease (high doses), Hyponatraemia

Specific considerations
Fluid and/or electrolyte imbalance, treatment with diuretics, NSAIDs or drugs known to induce SIADH, or at risk of increased intracranial pressure: take precautions to avoid hyponatraemia and/or fluid overload.
Renal impairment: Creatinine clearance <50 mL/minute, although use of tablets is contraindicated by the manufacturer, it is used IV in specialist centres in patients with factor VIII deficiency or end stage renal failure to correct bleeding time before certain procedures.
Pregnancy: Seek specialist advice; ADEC category B2.
Breastfeeding: Safe to use.

Adverse effects
Common: headache, nausea, abdominal cramps, hyponatraemia, Injection, pain and swelling at injection site
Infrequent: water intoxication, seizures

Dosage

Diabetes insipidus
Adult
Intranasal, 10–40 micrograms daily in 1 or 2 doses.
SC/IM/IV, 1–4 micrograms daily in 1 or 2 doses
Oral, 100–200 micrograms 3 times daily (range 200 micrograms – 1.2 mg daily).
Child
Intranasal, 2.5–20 micrograms daily in 1 or 2 doses
SC/IM/IV, up to 0.4 micrograms 3 times daily.
Oral, 100–200 micrograms 3 times daily

**Renal function testing**
Adult, intranasal, up to 40 micrograms; parenteral, up to 4 micrograms.
Child, intranasal, up to 20 micrograms
Infant, intranasal, up to 10 micrograms.
Dose equivalence: Intranasal dosage is approximately 10 times parenteral dosage.

**Counselling**
Tell your doctor immediately if you have headache, nausea, vomiting or weight gain

**Practice points**
- spray or rhinyle delivery system (supplied with nasal solution and gives more flexibility in dosage than the spray) can be used for nasal administration
- for diabetes insipidus, the larger dose is usually given at night to prevent nocturia and the smaller dose during the day
- restrict fluid intake when giving desmopressin for renal function testing or nocturnal enuresis
- monitor water balance, especially when the response to thirst is not functioning (eg sedated, unconscious or postoperative patients) or in patients with craniopharyngiomas or hypothalamic lesions

**Products**
DESMOPRESSIN TABS 0.2 MG (AS ACETATE) (MINIRIN®)

### 06.06.04 Dopamine agonists

Bromocriptine is a stimulant of dopamine receptors in the brain; it also inhibits release of prolactin by the pituitary. Bromocriptine is used for the treatment of galactorrhoea and cyclical benign breast disease, and for the treatment of prolactinomas (when it reduces both plasma prolactin concentration and tumour size). Bromocriptine also inhibits the release of growth hormone and is sometimes used in the treatment of acromegaly, but somatostatin analogues (such as octreotide) are more effective.

Cabergoline has actions and uses similar to those of bromocriptine, but its duration of action is longer. Its side-effects appear to differ from that of bromocriptine and patients intolerant of bromocriptine may be able to tolerate cabergoline (and vice versa).

**Fibrotic reactions**
The CSM has advised that ergot-derived dopamine-receptor agonists, bromocriptine, cabergoline, lisuride, and pergolide have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Before starting treatment with these ergot derivatives it may be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful.

Quinagolide has actions and uses similar to those of ergot-derived dopamine agonists, but its side-effects differ slightly.

**Suppression of lactation**
Although bromocriptine and cabergoline are licensed to suppress lactation, they are not recommended for routine suppression (or for the relief of symptoms of postpartum pain and engorgement) that can be adequately treated with simple analgesics and breast support. If a dopamine-receptor agonist is required, cabergoline is preferred.

Quinagolide is not licensed for the suppression of lactation.

**Sudden onset of sleep**
Excessive daytime sleepiness and sudden onset of sleep can occur with dopaminergic drugs. Patients starting treatment with these drugs should be warned of the possibility of these effects and of the need to exercise caution when driving or operating machinery.

Patients who have suffered excessive sedation or sudden onset of sleep, should refrain from driving or operating machines, until those effects have stopped recurring.
**BROMOCRIPTIN**

**Mode of action**
Stimulate dopamine receptors; inhibit prolactin secretion; reduce size of prolactinomas; decrease growth hormone concentration in people with acromegaly.

**Indications**
Acromegaly where surgery or radiotherapy are contraindicated or failed to control disease, or until radiotherapy becomes fully effective
Hyperprolactinaemia, including prolactinomas
Prevention of onset of lactation in the puerperium for clearly defined medical reasons
Parkinson's disease

**Contraindications**
Symptoms and/or history of serious psychiatric disorders
Pre-eclampsia, postpartum hypertension

**Specific considerations**
Treatment with ergot alkaloids, vasoconstrictive sympathomimetics: possible increased risk of cardiovascular adverse effects; avoid combination.
Compromised cerebral or cardiac circulation: risk of hypotension and collapse.
Peptic ulcer: risk of gastric haemorrhage in people with acromegaly.
Dopamine antagonists (eg some antipsychotics, metoclopramide): avoid combined use (mutual antagonism).
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Inhibits lactation. Bromocriptine should not be used for suppression of established lactation because of possible severe adverse effects, eg stroke.
Hepatic impairment: Limited data; dosage reduction may be required in severe impairment.

**Adverse effect**
Common: nausea, vomiting, abdominal pain, constipation, headache, dizziness, orthostatic hypotension, weakness, fatigue, nasal congestion, digital vasospasm, erythromelalgia, dyskinesia, psychiatric disorders (hallucination, confusion, delusion, psychotic episode), drowsiness, sudden sleep onset (particularly in patients with Parkinson's disease)
Rare: pleural effusion, retroperitoneal fibrosis (long term treatment with high doses of the ergot-derived dopamine agonists); gastric haemorrhage (in patients with acromegaly); hypertension, MI, seizure, stroke (in patients receiving bromocriptine for suppression of lactation); cardiac valvulopathy (infrequent with pergolide)

**Dosage**
Acromegaly
1.25 mg daily, increased gradually up to 10–30 mg daily according to response.

Hyperprolactinaemia
1.25 mg 2–3 times daily, increased gradually up to 2.5 mg 2–3 times daily according to response (up to 15 mg daily in divided doses in prolactinomas).

Prevention of onset of lactation
2.5 mg twice daily for 14 days (not until 4 hours after delivery and when vital signs are stable).

**Counselling**
Daily doses should be taken at night, especially when starting treatment.
Sometimes bromocriptine's side effects can be made worse by taking alcohol; avoid alcohol if this happens to you. This medicine may cause dizziness or drowsiness; if affected, do not drive or operate machinery.
Be careful when you stand up as this medicine might make you feel dizzy if you stand up too quickly.
Take with food to lessen the chance of nausea or stomach upset.

**Practice points**
- start treatment at low dose with the evening meal and increase gradually to limit adverse effects
- consider contraceptive measures if pregnancy is unwanted in women treated for hyperprolactinaemia; oral hormonal contraceptives are safe to use when plasma prolactin concentration is in the normal range
- monitor for pituitary enlargement, particularly during pregnancy (eg by checking visual fields)
- monitor for symptoms of progressive fibrotic disorders in patients on long term treatment with ergot-derived dopamine agonists

**Products**
BROMOCRIPTINE TABS 2.5 MG (AS MESILATE) (PARLODEL®, RONALIN®, SEDACORON®)
CABERGOLINE

Mode of action
Same as Bromocriptin

Indications
Same as Bromocriptin

Contraindications
Same as Bromocriptin

Specific considerations
Treatment with ergot alkaloids: possible increased risk of cardiovascular adverse effects; avoid combination.
Pregnancy: Limited data available; ADEC category B1.
Breastfeeding: Inhibits lactation.
Compromised cerebral or cardiac circulation: risk of hypotension and collapse.
Peptic ulcer: risk of gastric haemorrhage in people with acromegaly.
Dopamine antagonists (eg some antipsychotics, metoclopramide): avoid combined use (mutual antagonism).
Hepatic impairment: Limited data; dosage reduction may be required in severe impairment.

Adverse effects
Common: nausea, vomiting, abdominal pain, constipation, headache, dizziness, orthostatic hypotension, weakness, fatigue, nasal congestion, digital vasospasm, erythromelalgia, dyskinesia, psychiatric disorders (hallucination, confusion, delusion, psychotic episode), drowsiness, sudden sleep onset (particularly in patients with Parkinson's disease)
Rare: pleural effusion, retroperitoneal fibrosis (long term treatment with high doses of the ergot-derived dopamine agonists); gastric haemorrhage (in patients with acromegaly); hypertension, MI, seizure, stroke (in patients receiving bromocriptine for suppression of lactation); cardiac valvulopathy (infrequent)

Dosage
Hyperprolactinaemia
0.5 mg each week in 1 or 2 doses, increase gradually by 0.5 mg at monthly intervals up to 2 mg each week.
Prevention of onset of lactation
1 mg as a single dose during the first day postpartum.

Counselling
This medicine may cause dizziness or drowsiness; if affected, do not drive or operate machinery.
Be careful when you stand up as this medicine might make you feel dizzy if you stand up too quickly.
Take with food to lessen the chance of nausea or stomach upset.

Practice points
Same as Bromocriptin

Products
CABERGOLINE TABS 0.5 MG (DOSTINEX®)

06.06.05 Male sex hormones and antagonists (Androgens and Anti-androgens)

06.06.05.01 Androgens
Androgens cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease. In the normal male they inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Androgens also have an anabolic action which led to the development of anabolic steroids.
Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism; they should not be given until the hypogonadism has been properly investigated. Treatment should be under expert supervision.
When given to patients with hypopituitarism they can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone which will stimulate spermatogenesis as well as androgen production.
Caution should be used when androgens or chorionic gonadotrophin are used in treating boys with delayed puberty since the fusion of epiphyses is hastened and may result in short stature.
Intramuscular depot preparations of testosterone esters are preferred for replacement therapy. Testosterone enantate, propionate or undecanoate, or alternatively Sustanon®, which consists of a mixture of testosterone esters and has a longer duration of action, may be used. Satisfactory replacement therapy can sometimes be obtained with 1 mL of Sustanon 250®, given by intramuscular injection once a month, although more frequent dose intervals are often
necessary. Implants of testosterone can be used for hypogonadism; the implants are replaced every 4 to 5 months. Menopausal women are also sometimes given implants of testosterone (in a dose of 50–100 mg every 4–8 months) as an adjunct to hormone replacement therapy.

**MESTEROLONE**

- **Mode of action**
  Same as Testosterone
- **Indications**
  Same as Testosterone
- **Contraindications**
  Same as Testosterone
- **Specific considerations**
  Same as Testosterone
- **Adverse effects**
  Same as Testosterone but spermatogenesis unimpaired.
- **Comparative information**
  All can cause virilisation in women and precocious sexual development in children (see Adverse effects). Testosterone should be used in preference to synthetic androgens in male hypogonadism due to either pituitary or testicular disease or following castration. Androgen replacement is important to prevent long term complications such as osteoporosis, in addition to maintaining sexual function.

**Practice points**

- androgens are misused by some athletes and body builders in an attempt to increase muscle mass; such misuse exposes these people to an increased risk of serious adverse effects

**Products**

MESTEROLONE TABS 25 MG (PROVIRON®)

**TESTOSTERONE**

- **Mode of action**
  Stimulate and maintain sexual function and characteristics in men.
- **Indications**
  Male hypogonadism due to either pituitary or testicular disease or following castration
  Delayed puberty in adolescent males
- **Contraindications**
  Prostate or breast cancer (in men)
  Pregnancy and breastfeeding
- **Specific considerations**
  Cardiovascular disorders, renal or hepatic impairment, epilepsy, migraine, diabetes: risk of fluid retention.
  Women: Avoid use; risk of severe adverse effects, including suppression of ovarian activity and menstruation, virilisation.
  Children: Use with extreme caution in boys; risk of inhibition of growth due to premature closure of epiphyses; do not use in girls except on specialist advise.
- **Adverse effects**
  Severe adverse effects result mainly from inappropriate use of androgens in women, children, athletes and body builders.
  Sodium and water retention, oedema, acne, gynaecomastia, impotence, testicular atrophy, priapism, inhibition of spermatogenesis, degenerative changes in seminiferous tubules, amenorrhoea, clitoral enlargement, impaired glucose tolerance, hypercalcaemia, polycythaemia, decreased clotting factors, increased LDL cholesterol, aggressive behaviour, psychotic symptoms, physical and psychological dependence, withdrawal symptoms, premature closure of epiphyses
  Adverse effects of physiological doses of testosterone are mainly related to the route of administration.
  GI adverse effects, eg oily stools, nausea (testosterone undecanoate); bleeding, infection, extrusion (implant).
  Skin irritation: Very common with patches; pre-treatment with a topical corticosteroid may reduce incidence.
  Testosterone gel is less irritating than the patches.
- **Dosage**
  Dosage should be adjusted according to clinical response and formulation.
- **Male hypogonadism**
Testosterone undecanoate, oral 120–160 mg daily in 2 divided doses for 2–3 weeks (if using an odd number of capsules daily, the morning dose should be bigger), then adjust, according to response, to 40–120 mg daily.

Testosterone implant, SC 100–600 mg every 4–5 months

Testosterone enanthate, initially, IM 250 mg every 2–3 weeks. Maintenance, 250 mg every 3–6 weeks

Testosterone esters, IM 100–250 mg every 2–3 weeks

Testosterone patch, apply 1 patch (5 mg/24 hours) each night. Adjust the dose using 2.5 mg/24 hours patches (usual range 2.5–7.5 mg daily).

Testosterone gel, apply 5 g (equivalent to testosterone 50 mg) once daily. Adjust dose, according to response, in increments of 2.5 g (use half a 5 g sachet); maximum 10 g daily.

**Delayed puberty**

Testosterone undecanoate, initially 40 mg once daily; maintenance 80–120 mg once daily.

Testosterone enanthate, IM 50–100 mg each month.

**Counselling**

Capsules: This medicine is absorbed best when taken with a meal, Swallow whole without chewing.

Patches: Apply at night to clean, flat, dry, unbroken skin, eg back, abdomen, thigh or upper arm (not the scrotum). Avoid oily or hairy skin (very hairy skin may be clipped to enable the patch to stick) and bony areas such as the hip or shoulder. Remove the old patch each night and apply a new patch to a different area, to reduce skin irritation.

Gel: Spread thinly onto clean, dry, healthy skin of the shoulder, arm or abdomen (not genitals). You don't need to rub it in but allow the gel to dry before getting dressed. Wash your hands thoroughly after using the gel and cover the area with clothing once the gel has dried. Do not allow others to touch the application area as there is potential for transfer of testosterone; shower before situations where skin-to-skin contact is likely.

**Practice points**

- testosterone undecanoate has variable oral bioavailability and short duration of action; it may be used when other routes of administration are poorly tolerated or not recommended
- enough testosterone to cause virilisation can be absorbed by children from skin contact with people using transdermal testosterone products; emphasise to patients the importance of others avoiding contact with the application area
- androgens are misused by some athletes and body builders in an attempt to increase muscle mass; such misuse exposes these people to an increased risk of serious adverse effects

**Products**

TESTOSTERONE AMPS 100 MG/AMP (AS ENANTATE) 1 ML AMP (NOT REGISTERED)

TESTOSTERONE AMPS 250 MG/AMP (AS ENANTATE) 1 ML AMP (SUSTANON®, TESTOVIRON®)

**06.06.05.02 Anti-androgens**

**CYPROMERONE**

Cyproterone acetate is an anti-androgen used in the treatment of severe hypersexuality and sexual deviation in the male. It inhibits spermatogenesis and produces reversible infertility (but is not a male contraceptive); abnormal sperm forms are produced. Fully informed consent is recommended and an initial spermatogram. As hepatic tumours have been produced in animal studies, careful consideration should be given to the risk/benefit ratio before treatment. Cyproterone acetate is also used as an adjunct in prostatic cancer and in the treatment of acne and hirsutism in women.

**Mode of action**

Competitive blockade at androgen receptors; inhibit androgen activity.

**Indications**

Advanced prostate cancer

Suppression of GnRH analogue-associated initial tumour flare

Hot flushes associated with orchidectomy or GnRH analogue

Reduction of sexual drive in men

Moderately severe-to-severe signs of androgenisation in women (hirsutism, alopecia, seborrhoea, acne), seek specialist advice

**Contraindications**

History of hepatic impairment, except if due to metastases

**Specific considerations**

Thromboembolic disease, sickle cell anaemia, diabetes with vascular disease: rare reports of thromboembolic events.

Severe chronic depression: cyproterone can cause depression.
Diabetes: altered carbohydrate metabolism; monitor blood glucose concentration.

**Adverse effects**
Common: nausea, vomiting, increased transaminase concentrations, impotence, reduced libido, hot flushes, body hair loss, sweating, gynaecomastia, breast pain, itch, weight changes, headache, mood changes, insomnia, lethargy, cognitive changes, fatigue, oedema, inhibition of spermatogenesis, reduced ejaculate volume
Infrequent: jaundice, hepatitis, allergic reactions, shortness of breath, diarrhoea, reduced adrenal function, depression
Rare: hepatic failure (sometimes fatal with cyproterone), thrombosis, pulmonary embolism, tachycardia, intra-abdominal haemorrhage, osteoporosis

**Dosage**
Advanced prostate cancer, suppression of GnRH analogue-associated initial tumour flare: Initially 100 mg 3 times daily; can reduce to twice daily.
Hot flushes with GnRH therapy or after orchidectomy: 100 mg daily, reducing to 50 mg daily or alternate days.
Reduction of sexual drive in men: 50 mg twice daily.

**Counselling**
Take this medicine after a meal.
This medicine may cause tiredness and difficulty concentrating; do not drive or operate machinery if this occurs.
You may get shortness of breath; see your doctor if this is troublesome.
See your doctor immediately if you notice yellowing of the skin or eyes, dark urine or itch.

**Practice points**
- monitor liver function tests at baseline, then every 6 months
- due to the risk of hepatotoxicity, the UK Committee on Safety of Medicines recommends that cyproterone use in prostate cancer be restricted to short courses unless patients are unresponsive to, or intolerant of, other treatments
  - when used with GnRH analogue to suppress tumour flare, start antiandrogens 2 weeks before GnRH analogue and continue for 2–4 weeks
  - if there is a risk of spinal cord compression or ureteric obstruction it is important to start antiandrogens first; consider orchidectomy for rapid castrate levels of androgen
  - monitor liver function tests at baseline, then at regular intervals, see individual monographs
  - transaminases usually return to normal with continued treatment; stop antiandrogen treatment if transaminase concentrations exceed 3 times upper limit of normal range
  - withdrawal of nonsteroidal antiandrogen should precede the use of more toxic treatments for hormone-refractory prostate cancer as paradoxical disease regression may occur

**Products**
**CYPRETERONE TABS 50 MG (AS ACETATE) (ANDROCUR®)**

06.06.06 Drugs for menopausal symptoms (HRT)

**CONJUGATED OESTROGENS**

**Mode of action**
A drop in production of endogenous oestradiol can lead to symptoms such as hot flushes, night sweats and urogenital atrophy. These symptoms can be relieved by administration of oestrogen in HRT. Progestogen reduces risk of endometrial carcinoma associated with unopposed oestrogen.

**Indications**
Menopausal symptoms, eg hot flushes (includes combination products with medroxyprogesterone)
Prevention of osteoporosis, when non-oestrogen treatment is inappropriate (includes combination products with medroxyprogesterone); controversial, see Postmenopausal osteoporosis
Female hypogonadism, seek specialist advice

**Contraindications**
Previous or active thromboembolic disorder
Unexplained uterine bleeding
Severe liver disease
Breast cancer or other oestrogen-dependent tumour
Cerebrovascular or coronary artery disease

**Specific considerations**
Pregnancy: Avoid use; ADEC category D.
History of breast cancer: although HRT is associated with an increased risk of breast cancer, there is uncertainty about the risk in patients with treated breast cancer, seek specialist advice.
Hypertension: may be exacerbated.
Diabetes: conflicting data on effects on glucose metabolism but no increased incidence of clinical diabetes.
Migraine: may be exacerbated or relieved.
Gall bladder disease: may be exacerbated.
Endometriosis: may be activated or exacerbated.
Epilepsy: higher dose of oestrogen may be needed, as antiepileptics may increase clearance of oestrogen; re-titrate oestrogen dose according to symptoms if necessary when changing treatment for epilepsy.
Smoking: increases risk of thromboembolism.
Uterine fibroids: fibroids may increase in size.
Jaundice during pregnancy or previous oestrogen use: may recur.
Acute Porphyria: may cause an attack; avoid if possible; oestrogens may be safe in replacement doses.
Hepatic impairment: Avoid use in severe impairment.
Surgery: When possible, stop HRT 4 weeks before elective surgery that has a significant risk of postoperative thromboembolism, as HRT may increase this risk.

Adverse effects
These vary according to dose, regimen and patient characteristics
Common: mastalgia, abnormal mammogram, headache, depression, change in libido, weight change, breakthrough bleeding, spotting, leg cramps, dry eye syndrome (oestrogen alone)
Infrequent: breast cancer, premenstrual-like syndrome, dementia, migraine, stroke, venous thromboembolism, pulmonary embolism, cardiovascular events, fluid retention, oedema, increased BP, endometrial hyperplasia, dry eye syndrome (combination HRT), acne, itch, nausea, increased triglycerides
Rare: gall stones, cholestatic jaundice, pancreatitis, glucose intolerance, galactorrhoea, visual changes, chloasma, hypersensitivity (angioedema, urticaria), ovarian cancer, endometrial cancer, enlargement of uterine fibroids, enlargement of hepatic haemangiomas

Breast cancer
The background incidence of breast cancer increases with age. Type of HRT and duration of use further increase the risk.
Recent studies have found:
- increase in breast cancer, seen within 3–4 years
- that, in contrast to previous studies, breast cancer was diagnosed at a more advanced stage (and was more likely to be fatal) for HRT users than for those taking placebo
- breast cancer risk was highest for those taking progestogen and oestrogen
- there was no evidence of a difference in breast cancer risk between sequential and continuous regimes, various routes of administration or different oestrogens or progestogens (risk with tibolone appears to be higher than for oestrogen alone and less than that of oestrogen and progestogen regimens)
- increased risk diminishes to that of never users after HRT has been stopped for 5 years.

Endometrial cancer
Oestrogen-only HRT is associated with an increased risk of endometrial hyperplasia and cancer. This risk is reduced by addition of a progestogen,

Venous thromboembolism (VTE)
Women using HRT are likely to have a 2- to 4-fold increased risk for idiopathic thromboembolism compared with non-users. In younger women without heart disease this small increase in incidence (from 1/10 000 to 3/10 000 per year) appears acceptable, but in older women, particularly with established cardiovascular disease, both risks (increased from 23/10 000 to 62/10 000 per year) and benefits need to be weighed more carefully.

Dosage
Combination regimens, give either continuously (with a progestogen for 10-14 days each month) or for cycles of 3 weeks with a 7 day break, with a progestogen for last 10 days of oestrogen.
Menopausal symptoms: Oral, 0.3–1.25 mg daily, use minimum dose to control symptoms.
Osteoporosis prevention: Oral, 0.625 mg daily.

Patient counselling
Tell your doctor immediately if you develop:
symptoms of a blood clot (red, swollen or painful leg, difficulty in breathing, or chest pain)
changes in your breasts (skin changes, lump, nipple changes)
changes in vaginal bleeding a few months after starting HRT (e.g. heavy or irregular bleeding, or bleeding after sex).

Practice points
- review need for treatment regularly (at least annually)
• withdraw HRT slowly, eg over 3–6 months, to minimise withdrawal symptoms
• choose vaginal preparations for women who only have urogenital symptoms
• irregular or atypical bleeding may indicate endometrial pathology and warrants further investigation
• HRT is not associated with improvement in quality of life (unrelated to relief of menopausal symptoms) and it is not effective for prevention of:
  o cardiovascular disease
  o dementia
  o anxiety or depression
• consider HRT for women without coronary heart disease (taking into account risks, eg VTE, cancer) to:
  o treat menopausal symptoms
  o prevent loss of bone mineral density and fractures in women at high risk of osteoporosis, when other treatments are inappropriate (however benefit does not appear to outweigh risks, even in these patients, unless vasomotor symptoms are very troublesome)
• consider need for progestogen carefully in women who have not had a hysterectomy; balance prevention of endometrial hyperplasia and reduced risk of endometrial carcinoma against the increased risk of breast cancer.
• women who dislike periods may benefit from:
  o reducing the oestrogen dose or
  o using continuous progestogen or
  o using a progestogen course once every 3 months (produces less frequent withdrawal bleeds)

Perimenopause
• HRT does not provide contraceptive protection; conception can still occur in the perimenopause even though fertility is reduced, see also Contraception
• consider low dose oral contraceptives (in preference to HRT products) until the menopause occurs, then if still needed, change to HRT
• vasomotor symptoms may occur during the pill-free week for oral contraceptives; symptoms may be reduced by tricycling packs or using HRT doses of oestrogen during this time

Products
CONJUGATED ESTR OGENS TABS 0.625 MCG (PREMARIN®)

CONJUGATED EQUINE ESTR OGENS V AGINAL CREAM 0.625 MG/GM 42.5 GM TUBE (PREMARIN CREAM®)

ESTRADIOL 1-2 MG + DYDROGESTERON 5-10 MG (FEMOSTON®, FEMOSTON CONTI®)

ESTRADIOL 2 MG + NOR GESTEROL 0.5MG TABS (PROGYLUTON®)
OESTRADIOL V AGINAL TABS 25 MCG (VAGIFEM®)
DYDROGESTERONE TABS 10 MG (DUPHASTON®)
TIBIOLONE TABS 2.5 MG (LIVIAL®)

06.06.07 Drugs for peripheral vascular disease

NICERGOLINE
Adverse Effects and Precautions
Adverse effects which may occur after nicergoline include gastrointestinal disturbances and, particularly after parenteral administration, hypotension.
Porphyria: Nicergoline is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in in-vitro systems, although there is conflicting evidence of porphyrinogenicity.
Uses and Administration
Nicergoline is an ergot derivative. It has been used similarly to co-dergocrine mesilate to treat symptoms of mental deterioration associated with cerebrovascular insufficiency and has also been used in peripheral vascular disease. Nicergoline has been given in doses of up to 60 mg daily by mouth in divided doses, and by intramuscular injection in doses of 2 to 4 mg twice daily; 4 to 8 mg daily has been given by slow intravenous infusion. Nicergoline tartrate has been used in preparations for parenteral administration.
Products
NICERGOLINE TABS 5 MG (SERGOLIN®, SERMION®)

PENTOXIFYLLINE (OXYPENTIFYLLINE)
Xanthine derivative
Mode of action
Vasodilator; reduces blood viscosity.
Indications
Symptom relief of claudication in patients with peripheral vascular disease unsuitable for surgical treatment
Specific considerations
Cerebral or retinal haemorrhage, peptic ulcer disease: may exacerbate bleeding; avoid use.
Acute MI: risk of arrhythmia; avoid use.
Renal impairment: Dosage reduction may be required in severe impairment.
Pregnancy: No data available; avoid use; ADEC category B1.
Breastfeeding: No data available; avoid use.
Adverse effects
Common: nausea, vomiting, dizziness, headache, flushing
Infrequent: angina, palpitations
Rare: hypersensitivity, itching, rash, urticaria, bleeding, hallucinations, arrhythmias, aseptic meningitis
Dosage
400 mg 2–3 times daily.
Counselling
Swallow tablet whole; do not crush or chew. Take with food to reduce stomach upset.
Products
PENTOXIFYLLINE TABS 400 MG (CIRCULAID®, OXYPHYL®, PENTOXINE®, PENTYLLIN®, TRENTAL®,)
PENTOXIFYLLINE TABS 600 MG (NOT REGISTERED)
### Table 06–01 Insulins: comparative information

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset of action (hours)</th>
<th>Time to peak activity (hours)</th>
<th>Duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ultra-short acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin lispro, insulin aspart</td>
<td>0.25</td>
<td>1</td>
<td>4–5</td>
</tr>
<tr>
<td><strong>short acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neutral</td>
<td>0.5</td>
<td>2–3</td>
<td>6–8</td>
</tr>
<tr>
<td><strong>intermediate acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-mixed</td>
<td>1–2.5</td>
<td>4–12</td>
<td>16–24</td>
</tr>
<tr>
<td>mixed with short acting insulin</td>
<td>0.5–1</td>
<td>2–12</td>
<td>16–24</td>
</tr>
<tr>
<td>mixed with ultra-short acting insulin</td>
<td>0.25</td>
<td>1</td>
<td>16–18</td>
</tr>
<tr>
<td><strong>long acting</strong></td>
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<tr>
<td>insulin glargine</td>
<td>1–2</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>non-mixed</td>
<td>2–4</td>
<td>10–20</td>
<td>24–36</td>
</tr>
</tbody>
</table>

### Table 06–02 Sulfonylureas: comparative information

<table>
<thead>
<tr>
<th>Sulfonylurea</th>
<th>Frequency of administration</th>
<th>Risk of hypoglycaemia</th>
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</thead>
<tbody>
<tr>
<td>glibenclamide</td>
<td>once or twice daily</td>
<td>high</td>
</tr>
<tr>
<td>glimepiride</td>
<td>once daily</td>
<td>high/intermediate</td>
</tr>
<tr>
<td>glipizide</td>
<td>once or twice daily</td>
<td>low/intermediate</td>
</tr>
<tr>
<td>gliclazide</td>
<td>once or twice daily</td>
<td>intermediate</td>
</tr>
</tbody>
</table>
COMBINED ORAL HORMONAL CONTRACEPTIVES (COCs)

**Mode of action**
All COCs contain an estrogen and progestagen. They inhibit ovulation, reduce receptivity of endometrium to implantation and thicken cervical mucus to form a barrier to sperm.

**Indications**
Marketed
Contraception.

Moderate acne (not controlled with topical agents) in women
Androgenisation (hirsutism and acne) in women (cyproterone with ethinyloestradiol).

Accepted
Emergency contraception (if levonorgestrel unavailable).
Menstrual disorders, e.g. dysfunctional uterine bleeding (heavy, irregular), period pain.
Endometriosis
Premenstrual syndrome

**Contraindications**
Pregnancy
Unexplained uterine bleeding.
History of, or hereditary predisposition for, thromboembolic disorders
Viral hepatitis, current; severe cirrhosis
History of breast, endometrial or hepatic cancer
History of cerebrovascular or coronary artery disease
Pulmonary hypertension, AF, history of subacute bacterial endocarditis.
Malabsorption syndrome (likely to be ineffective), except cystic fibrosis
Migraine and age >35 years or migraine with aura

**Specific considerations**
Diabetes: conflicting data on effects on glucose metabolism but no increased incidence of clinical diabetes; avoid use in pre-existing end organ damage; additional risk of thrombosis.
Hypertension: may be exacerbated; monitor regularly; avoid use if BP is not controlled.
Depression: may worsen; balance this risk against the risk of pregnancy exacerbating depression.
Epilepsy: higher doses of oral contraceptive will be required with concurrent enzyme-inducing antiepileptic medication.
Migraine and age >35 years: migraine may be exacerbated or relieved (COCs are contraindicated in migraine with aura due to increased risk of stroke).
Cholestatic jaundice of pregnancy or with previous oral contraceptive use: increases risk of jaundice.
Smoking (especially age >35 years): increases risk of thromboembolism and cardiovascular events; advise an alternative method of contraception or stop smoking.
Familial hyperlipidaemia: may increase serum concentrations of cholesterol and triglycerides.
Postpartum, not breastfeeding: increases risk of thromboembolism if started <3 weeks after birth.
Acute Porphyria: may cause an attack; seek specialist advice.
Hepatic impairment: Avoid use in severe impairment.
Surgery: Estrogen component of COC may increase the risk of thromboembolism. Stop the combined pill 4 weeks before major elective surgery and all leg surgery; progestogen-only pill may be considered. If the patient is still taking an estrogen-containing pill at the time of surgery, heparin prophylaxis may be appropriate.
Pregnancy: No increased risk of birth defects from exposure in early pregnancy (except possibly for cyproterone-containing pills); ADEC category B3.
Breastfeeding: Oestrogens may decrease milk supply; avoid use (progestogen-only contraceptive is preferred). May be considered from 6 months postpartum if breastfeeding is established and other contraceptive methods are unacceptable.
Adverse effects
Tolerance to adverse effects often develops during the first 3 months of use. Breakthrough bleeding is likely to stop by the end of the third month.

The benefits of oral contraception often outweigh the risks; benefits include prevention of pregnancy and its complications, regular and reduced menstrual loss (reducing the risk of iron deficiency anaemia), reduced risk of ovarian and endometrial carcinoma, reduced risk of ovarian cysts.

Common: breakthrough bleeding, nausea, vomiting, changes in weight, breast enlargement and tenderness, headache, mood changes (e.g. depression), changes in libido, fluid retention, chloasma, acne, thrush

Infrequent: amenorrhoea, contact lens intolerance, rash, hirsutism, alopecia, decreased glucose tolerance (especially with levonorgestrel-containing pills) but no evidence of increased incidence of clinical diabetes

Rare: allergy (e.g. urticaria, angioedema), hypertension, VTE (see Venous thromboembolism), pulmonary embolism, stroke, jaundice, pancreatitis, hepatic adenoma, cervical cancer (see Cervical cancer), photosensitivity.

The risk of VTE depends on the dose of estrogen, the progestogen and the presence of other risk factors:

Risk of VTE per 100 000 patient-years is approximately:
- 5 to 10 for non-users
- 20 for COCs containing either levonorgestrel or norethisterone with 30–35 micrograms ethinyloestradiol
- 40 for COCs containing desogestrel or gestodene.
- 80 for COCs containing cyproterone
- 80 during pregnancy
- 95 for COCs containing 50 micrograms ethinyloestradiol.

Breast cancer: It is still unclear whether there is an increased risk of breast cancer among users of the COC.

Cervical cancer: Long term COC use (>5 years) may be associated with an increased risk of cervical cancer in human papilloma virus-positive women. Encourage regular cervical screening especially in women taking the COC.

Drug choice

Progestogen

Levonorgestrel, norethisterone

These progestogens have been used in COCs for many years. COCs containing these are associated with a lower risk of VTE than other COCs.

Gestodene, desogestrel

They have less androgenic activity than levonorgestrel, however, COCs containing gestodene or desogestrel have approximately twice the risk of VTE compared to COCs containing levonorgestrel or norethisterone.

They are generally not first choice for new users but may be used for those not tolerating other progestogens, providing estimates of incidence of venous thromboembolism are given to the woman.

Drospirenone

Related to spironolactone, this progestogen has anti-mineralocorticoid (mild diuretic and potassium retention) activity. Combined with ethinyloestradiol (Yasmin®), it has similar effects on the skin, contraceptive efficacy and cycle control to COCs containing gestodene or desogestrel; compelling evidence is lacking for any particular benefit for Yasmin®, eg less weight gain or reduced androgenic effects. The incidence of VTE with this COC appears to be similar to COCs containing levonorgestrel. It is unclear whether it can cause hyperkalaemia if used in women with renal impairment or taking drugs which increase potassium concentration.

Cyproterone

Progestogenic and anti-androgenic: It is used with an oestrogen to treat women with androgenisation (eg severe acne, idiopathic hirsutism); the combination also provides effective contraception. This combination is associated with a higher incidence of venous thromboembolism compared to other COCs and is not indicated as a COC in the absence of androgenisation.

Regimen

Available as monophasic (fixed) or triphasic regimens, and low, standard or high dose oestrogen formulations

Triphasic regimens are more complex and may be associated with cyclical symptoms, eg fluid retention, premenstrual syndrome; no advantage over monophasic regimens has been demonstrated.

In general, start contraception with a standard dose preparation. They are as effective as high dose, except in specific groups, eg women taking hepatic enzyme-inducing drugs such as antiepileptics.

Monophasic oral contraceptives

Each active tablet contains the same doses of oestrogen and progestogen.

‘Tricycling’ may be used for women with headaches or other symptoms in the withdrawal week, heavy or painful periods, epilepsy or endometriosis. This involves having a pill-free interval of 3–7 days only once every 3 months (missing inactive tablets for 2 months). This regimen will decrease the frequency of menses.
Standard dose: contain 30–35 micrograms ethinyloestradiol or 50 micrograms of mestranol. Generally the preferred strength of COC; as effective as those containing 50 micrograms ethinyloestradiol; the lower dose of oestrogen reduces the risk of adverse cardiovascular effects. Associated with a higher incidence of intermenstrual bleeding initially than high dose preparations and unlikely to be effective when used with hepatic enzyme inducers (eg phenytoin, carbamazepine, and rifampicin).

Low dose: contain 20 micrograms ethinyloestradiol with 100 micrograms levonorgestrel. Low dose preparations are as effective as standard dose, with a slightly higher incidence of breakthrough bleeding, especially at first.

High dose: contain 50 micrograms ethinyloestradiol. Risk of adverse effects is increased compared to lower dose preparations. Useful for contraception in women experiencing persistent breakthrough bleeding with the standard dose oral contraceptive (for >3–6 months); and for the treatment of dysfunctional uterine bleeding. May also be used for contraception in women taking hepatic enzyme-inducing drugs (where there is reduced efficacy of oral contraceptive) although there is still a risk of contraceptive failure.

Triphasic oral contraceptives

Oestrogen and progestogen content varies throughout the cycle. The dose of oestrogen is usually increased in the middle of the cycle to lower the rate of breakthrough bleeding. The progestogen dose is low initially but usually increases stepwise as the cycle progresses.

Administration instructions

For immediate contraceptive effect all COCs should be started in the first week of active tablets on day 1-5 of menses. Packets vary in presentation; many brands start with inactive pills, depending on the day of the week.

Women should be shown which are active (hormonal) and which are inactive tablets.

Patient counselling

If you start with an active pill within the first 5 days of your period you are protected from pregnancy immediately. If you start active pills after this time use additional contraception, e.g. condoms, or avoid vaginal intercourse until you have taken 7 active pills.

Effectiveness of the pill may be reduced by:

- Taking additional medications
- Vomiting or diarrhoea (which also may be caused by some medications), see Missed pills
- Taking St John’s Wort.

Ask your doctor or pharmacist if any other medications you are taking are likely to have an effect on the pill.

If you are over 35 years and smoke, you have a greater risk of developing a blood clot while taking the pill. Consider alternative contraception or stop smoking.

If any of the following symptoms occur while on the pill, stop taking it and seek urgent medical advice: severe and sudden pain in the chest, severe headache, sudden blurred vision or loss of sight, unexplained tenderness or pain and swelling in one leg.

Your period should start during the pill-free week if using a 21-day pack, or when taking the inactive tablets if using a 28-day pack. Do not extend the inactive tablet/pill-free week as it will increase your risk of pregnancy.

Missed pills

If you forget to take an inactive pill, contraception will not be affected.

If you miss an active pill by <12 hours, take it as soon as you remember and take the next pill at the usual time; contraception will not be affected.

If you miss an active pill by >12 hours, or if you have severe vomiting or diarrhoea, the pill will not be as effective in preventing pregnancy:

- take it as soon as you remember and take the next pill at the usual time
- continue with the daily pill but use another contraceptive method (e.g. condoms) or avoid intercourse for 7 days of active pill taking
- if the 7 days extend into the inactive pill/pill-free week, do not have a break from taking active pills; finish the active pills in your present pack then proceed on to the active pills in a new pack (your menstrual period will be delayed until the end of the new pack, unless you are taking a triphasic pill, in which case you may still spot or bleed).

Emergency contraception

If it is necessary to take your pill and an emergency contraceptive tablet (ie missed pill and unprotected intercourse), treat the emergency contraceptive as 1 dose of your pill, and then continue pill pack as usual.

Changing preparations

Changing from a COC pill to a higher or same dose pill, take as normal including the inactive pills.

Changing from a COC pill to a lower dose pill, miss any inactive pills and start taking the new pill without an inactive pill/pill-free interval.
Changing from a progestogen-only pill to a COC pill, start taking the active pill without any interval. Changing from a COC pill to a progestogen-only pill, depot injection or implant, start the progestogen-only pill, depot injection or insert implant on day immediately following the last active tablet in your current pack.

**Practice points**
- although indicated for premenstrual syndrome (PMS), COCs can also worsen or cause PMS (may be more likely with triphasic regimens)
- before prescribing the pill take a thorough history and examination, including BP
- ensure long term users of COCs are included in cervical screening program
- there may be a delay of 1–2 months before return of menstrual periods after stopping the COC

**CYPROTERONE WITH ETHINYLESTRADIOL**

**Mode of action**
Same as COCs

**Indications**
Androgenisation (mild-to-moderate hirsutism or severe acne) and contraception in these women
Other indications: same as COCs

**Contraindications**
Contraception in absence of androgenic symptoms
Other contraindications: same as COCs

**Specific considerations**
Pregnancy
Cyproterone has anti-androgenic effects; ADEC category B3.
Other specific considerations; same as COCs

**Adverse effects**
Same as COCs

**Dosage**
One tablet daily.

**Administration instructions**
Same as COCs

**Patient counselling**
Same as COCs

**Practice points**
- stop treatment 3–4 cycles after the androgen-related condition has completely resolved
- this combination is associated with a markedly increased risk of venous thromboembolism compared with other COCs
- although indicated for premenstrual syndrome (PMS), COCs can also worsen or cause PMS (may be more likely with triphasic regimens)
- before prescribing the pill take a thorough history and examination, including BP
- ensure long term users of COCs are included in cervical screening program
- there may be a delay of 1–2 months before return of menstrual periods after stopping the COC

**Products**
CYPROTERONE 2 MG+ETHINYLESTRADIOL TABS 0.035 MG (AS ACETATE) (DIANE 35®)

**LEVONORGESTREL WITH ETHINYLESTRADIOL**

**Mode of action**
Same as COCs

**Indications**
Moderate acne (not controlled with topical agents) in women

**Contraindications**
Same as COCs

**Specific considerations**
Same as COCs

**Adverse effects**
Same as COCs
Dosage
One tablet daily for 21 or 28 days. If using a 21-day pack, this is followed by a pill-free week.

Administration instructions
Same as COCs

Patient counselling
Same as COCs

Practice points
- may be considered for emergency contraception (Yuzpe regimen) if levonorgestrel is not available:
  - give 4 tablets of levonorgestrel 150 micrograms with ethinylestradiol 30 micrograms as soon as possible after unprotected intercourse, followed 12 hours later by a further 4 tablets, see also Emergency contraception
  - consider giving an antiemetic, e.g. metoclopramide, 30–60 minutes before each dose
- although indicated for premenstrual syndrome (PMS), COCs can also worsen or cause PMS (may be more likely with triphasic regimens)
- before prescribing the pill take a thorough history and examination, including BP
- ensure long term users of COCs are included in cervical screening program
- there may be a delay of 1–2 months before return of menstrual periods after stopping the COC.

Products
LEVONORGESTREL+ ETHINYLESTRADIOL SET (MICROGYNON®, NORDETTE®, NORDIOL®, TRINORDIOL®)

NORETHISTERONE WITH ETHINYLESTRADIOL

Mode of action
Same as COCs

Indications
Contraception

Contraindications
Same as COCs

Specific considerations
Same as COCs

Adverse effects:
Same as COCs

Dosage
One tablet daily for 21 or 28 days. If using a 21-day pack, this is followed by a pill-free week.

Administration instructions
Same as COCs

Patient counselling
Same as COCs

Practice points
- although indicated for premenstrual syndrome (PMS), COCs can also worsen or cause PMS (may be more likely with triphasic regimens)
- before prescribing the pill take a thorough history and examination, including BP
- ensure long term users of COCs are included in cervical screening program
- there may be a delay of 1–2 months before return of menstrual periods after stopping the COC.

Products
NORETHISTERONE + ETHINYLESTRADIOL SET (ACTIVELLE®, KLIOGEST®)

07.01.02 PROGESTOGEN ONLY

NORETHISTERONE

Mode of action
Thin and change endometrium to prevent implantation and thicken cervical mucus to impede the passage of sperm
They act on hypothalamus and suppress pituitary luteinising hormone surge and may inhibit ovulation. Depot injection and implant reliably suppress ovulation; oral progestogen-only contraceptive suppresses ovulation in <50% of women. Levonorgestrel-releasing IUD has a more local effect on endometrium and ovulation is suppressed in
some women.

**Indications**

Contraception, either as progestogen-only contraceptive or as a component of a COC

HRT as adjunct to estrogen.

Endometriosis

Delay of menstruation.

Menstrual disorders e.g. dysfunctional uterine bleeding

Contraception when estrogen-containing products are not tolerated or are unsuitable, e.g. breastfeeding, history of thromboembolic disorders, smokers.

**Contraindications**

Pregnancy

Breast cancer or liver cancer

Hepatitis, active viral; severe cirrhosis

**Specific considerations**

Malabsorption syndromes: oral progestogen-only contraceptives are contraindicated because of reduced efficacy.

Abnormal vaginal bleeding: avoid until fully investigated, as progestogens cause irregular vaginal bleeding.

Acute Porphyria: may cause an attack; seek specialist advice.

Postpartum: if used as contraceptive before 3 weeks postpartum may cause heavy, irregular bleeding

Surgery: May be used before major elective surgery; minimal risk of thromboembolic events unless other cardiovascular risk factors are present.

Pregnancy: Contraception, use in early pregnancy has not been associated with an increased risk of birth defects. Note that a pregnancy due to contraceptive failure is more likely to be ectopic. ADEC category B3.

Other indications, avoid use; virilisation of female fetus if taken by the mother at or after 8 weeks after conception; no adverse effects before this; ADEC category D.

Breastfeeding: Preferred hormonal contraceptives for breastfeeding women; do not inhibit lactation.

**Adverse effects**

Common: menstrual irregularity, prolonged bleeding, spotting, amenorrhoea, depression, weight gain.

Infrequent: nausea, vomiting, headache, dizziness, lethargy, breast discomfort.

Rare: cholestatic jaundice, decreased libido, androgenic effects (acne, greasy hair), anaphylactic reaction.

**Dosage**

Contraception: 350 micrograms daily beginning on the first or second day of menstruation or day 21 postpartum.

Delay of menstruation: Start 3–5 days before expected menstruation. 5 mg 2–3 times daily for up to 14 days (bleeding starts 2–3 days after stopping tablets).

Dysfunctional uterine bleeding: To stop bleeding, 5 mg 3 times daily for 10 days. Higher doses have been used in certain cases, seek specialist advice. To regulate bleeding, 5 mg once or twice daily for days 16–25 of cycle.

Endometriosis: 5–10 mg once daily. Continue treatment for at least 4-6 months.

HRT: 1.25 mg daily for 10–14 days of cycle with daily estrogen.

**Patient counseling**

**Contraception**

Take pills at about the same time (within 3 hours) every day. Choose a time when you are most likely to remember, and keep to it. Use additional contraception for 48 hours if starting after first or second day of menstruation.

Must be taken continuously; there are no inactive (sugar) pills or a 7-day break as with the combined pill.

If you miss a pill, take it as soon as you remember and carry on with the next pill at the usual time. If the pill is >3 hours overdue, you are not protected. Resume normal pill taking, but use another contraceptive method, e.g. condoms, for the next 48 hours. If unprotected intercourse has occurred, emergency contraception should be used.

Vomiting, very severe diarrhoea, a forgotten pill (>3 hours late) and other medications may stop the pill from working. Effective contraception will be assured 48 hours after restarting the pill; use another contraceptive method in the meantime.

Taking rifampicin or rifabutin may decrease the effectiveness of your pill; use additional non-hormonal contraception, e.g. condoms, during treatment with the antibiotic and for 4 weeks after.

**Practice points**

- there is no reliable evidence for the efficacy of norethisterone in the treatment of premenstrual syndrome.

**Contraception**

- less effective than the COC.
• if started on the first or second day of a period, no additional contraception is required; if started at any other time, it is not effective until after 48 hours; in this case, use additional contraception for the first 2 days of pill taking
• consider the possibility of ectopic pregnancy in cases of contraceptive failure; progestogen-only contraceptives do not reliably inhibit ovulation and therefore offer less protection against ectopic than intrauterine pregnancy (in trials for 1 brand up to 10% of pregnancies were ectopic)
• consider using copper or levonorgestrel-releasing IUD or depot medroxyprogesterone for women taking medication which increases the metabolism of progestogen-only contraceptives.

Products
NORETHISTERONE TABS 5 MG (AS ACETATE) (AMINOR®, PRIMOLUT NOR®)

PROGESTERONE
HYDROXYPROGESTERON
MEDROXYPROGESTERONE

Mode of action
Same as Norethisterone.

Indications
Contraception (IM depot)
Dysfunctional uterine bleeding (oral)
Secondary amenorrhoea (oral)
Endometriosis
HRT (as adjunct to oestrogen), for combination products, see Conjugated equine oestrogens

Contraindications
Pregnancy
Breast cancer or liver cancer
Hepatitis, active viral; severe cirrhosis

Specific considerations
Adolescents: reduction in bone mineral density with IM depot (during the period when peak bone mass is usually attained) may be more significant than in adults; avoid using as contraceptive of first choice if possible.
Abnormal vaginal bleeding: avoid until fully investigated, as progestogens cause irregular vaginal bleeding.
Acute Porphyria: may cause an attack; seek specialist advice.
Postpartum: if used as contraceptive before 3 weeks postpartum may cause heavy, irregular bleeding.
Surgery: May be used before major elective surgery; minimal risk of thromboembolic events unless other cardiovascular risk factors are present.
Pregnancy: IM, no harmful effects on fetus even in early pregnancy; ADEC category A.
Oral (daily dose >30 mg), theoretically could cause virilisation of female fetus if taken from 8 weeks after conception; effect is unlikely as medroxyprogesterone is not a 19-nortestosterone derivative; ADEC category D.
Breastfeeding: Preferred hormonal contraceptives for breastfeeding women; do not inhibit lactation.

Adverse effects
Common: menstrual irregularity, spotting, amenorrhoea, breast discomfort, abdominal cramps, bloating, oedema, weight gain, headache, dizziness, vaginal irritation.
Rare: thromboembolism.

Dosage
Pessaries, usual range 100–200 mg twice daily. Maximum of 400 mg twice daily. Start within several days of ovulation and continue for up to about 11 weeks if pregnancy occurs.
Vaginal gel, insert 1 applicatorful into the vagina once or twice daily. Start within 2–4 days of HCG administration and continue until at least 2 days after positive pregnancy test, then consider continuing for up to 8–10 weeks.

Practice points
• do not use other vaginal therapies during treatment with progesterone
• vaginal bleeding or threatened miscarriage may occur if progesterone is stopped suddenly in early pregnancy
• monitor beta-human chorionic gonadotrophin (b-HCG) concentrations to detect a non-viable pregnancy
• a recent study found that progesterone pessaries reduced the incidence of preterm birth in women at increased risk.
07.01.03 OTHER CONTRACEPTIVES

COPPER IUD

Mode of action
Interfere with sperm movement (preventing fertilisation) and with implantation of fertilised ovum.

Indications
Marketed: Contraception in women at minimal risk of STIs, including nulliparous women, when other methods are not tolerated
Accepted: Emergency contraception.

Contraindications
Pregnancy
Pelvic inflammatory disease (PID) or STI (current or within 3 months).
Anatomically distorted uterus

Specific considerations
Nulliparity: carefully assess the risk/benefit ratio in young nulliparous women; may be more difficult to insert IUD and risk of expulsion is higher.
Women at risk of contracting STIs: PID and its complications may be more likely.
Postpartum: do not insert until 6 weeks after delivery as there is an increased risk of uterine perforation.
Abnormal vaginal bleeding, recent abnormal Pap smear: avoid insertion of IUD until investigated.
Breastfeeding: Take particular care during insertion. During lactation there is a theoretical increase in risk of uterine perforation.

Adverse effects
Common: period pain, increased menstrual flow with possible menorrhagia, expulsion of device (particularly in the first year).
Infrequent: pelvic infection (in first 3 weeks after insertion), uterine perforation.
PID: Risk of PID with modern copper IUDs is low and is related to the risk of STI, i.e. PID is rare when risk of STI is low.

Dosage
Insert device according to the manufacturer’s instructions; replace every 5 or 8 years.

Patient counselling
If there are harmful bacteria present in your vagina the IUD can increase the chance of a pelvic infection. It is most likely in the 3 weeks after the IUD is fitted (but can happen at other times). If it is not treated the infection may cause PID. See a doctor if you have signs of an infection, such as unusual discharge or pain.
Check for presence and length of IUD string as it may be expelled unnoticed.

Practice points
- give an oral analgesic an hour before insertion (procedure often causes temporary discomfort similar to period pain)
- women at highest risk of pelvic infection with an IUD are those with risk factors for STIs, a history of pelvic infection and nulliparous women <25 years
- may be used to provide emergency contraception if inserted up to 120 hours (5 days) after intercourse; can also be inserted >5 days after intercourse provided the time of ovulation can be estimated and insertion does not occur >5 days after ovulation; provides ongoing contraception if left in situ
- if pregnancy occurs with IUD in situ consider the possibility of ectopic pregnancy; there is also an increased risk of spontaneous abortion and sepsis; remove device as soon as possible in first trimester
- magnetic resonance imaging (MRI) will not affect a copper IUD and an MRI scan will not be impaired by the presence of an IUD

07.01.04 DRUGS FOR MENOPAUSAL SYMPTOMS (HRT)
CONJUGATED EQUINE ESTROGENS

Mode of action
A drop in production of endogenous estradiol can lead to symptoms such as hot flushes, night sweats and urogenital atrophy. These symptoms can be relieved by administration of estrogen in HRT. Progestogen reduces risk of endometrial carcinoma associated with unopposed estrogen.

Indications
Menopausal symptoms (e.g. hot flushes).
Prevention of osteoporosis, when non-estrogen treatment is inappropriate; controversial
Female hypogonadism; seek specialist advice.

Contraindications
Previous or active thromboembolic disorder
Unexplained uterine bleeding.
Severe liver disease
Breast cancer or other estrogen-dependent tumour
Cerebrovascular or coronary artery disease

Specific considerations
History of breast cancer: although HRT is associated with an increased risk of breast cancer, there is uncertainty about the risk in patients with treated breast cancer, seek specialist advice.
Hypertension: may be exacerbated.
Diabetes: conflicting data on effects on glucose metabolism but no increased incidence of clinical diabetes.
Migraine: may be exacerbated or relieved.
Gall bladder disease: may be exacerbated.
Endometriosis: may be activated or exacerbated.
Epilepsy: higher dose of estrogen may be needed, as antiepileptics may increase clearance of estrogen; re-titrate estrogen dose according to symptoms if necessary when changing treatment for epilepsy.
Smoking: increases risk of thromboembolism.
Uterine fibroids: fibroids may increase in size.
Jaundice during pregnancy or previous estrogen use: may recur.
Acute Porphyria: may cause an attack; avoid if possible; oestrogens may be safe in replacement doses.
Hepatic impairment: Avoid use in severe impairment.
Surgery: When possible, stop HRT 4 weeks before elective surgery that has a significant risk of postoperative thromboembolism, as HRT may increase this risk.
Pregnancy: Avoid use; ADEC category D.

Adverse effects
These vary according to dose, regimen and patient characteristics, see also Table 7–3 Management of HRT adverse effects.
Common: mastalgia, abnormal mammogram, headache, depression, change in libido, weight change, breakthrough bleeding, spotting, leg cramps, dry eye syndrome (estrogen alone).
Infrequent: breast cancer, premenstrual-like syndrome, dementia, migraine, stroke, venous thromboembolism, pulmonary embolism, cardiovascular events, fluid retention, oedema, increased BP, endometrial hyperplasia, dry eye syndrome (combination HRT), acne, itch, nausea, increased triglycerides.
Rare: gall stones, cholestatic jaundice, pancreatitis, glucose intolerance, galactorrhoea, visual changes, chloasma, hypersensitivity (angioedema, urticaria), ovarian cancer, endometrial cancer, enlargement of uterine fibroids, enlargement of hepatic haemangiomas.
Breast cancer: The background incidence of breast cancer increases with age. Type of HRT and duration of use further increase the risk.

Recent studies have found:
- increase in breast cancer, seen within 3–4 years
- that, in contrast to previous studies, breast cancer was diagnosed at a more advanced stage (and was more likely to be fatal) for HRT users than for those taking placebo
- breast cancer risk was highest for those taking progestogen and estrogen
- there was no evidence of a difference in breast cancer risk between sequential and continuous regimes, various routes of administration or different oestrogens or progestogens (risk with tibolone appears to be higher than for estrogen alone and less than that of estrogen and progestogen regimens)
- increased risk diminishes to that of never users after HRT has been stopped for 5 years.
Endometrial cancer: Estrogen-only HRT is associated with an increased risk of endometrial hyperplasia and cancer. This risk is reduced by addition of a progestogen.

Venous thromboembolism (VTE): Women using HRT are likely to have a 2- to 4-fold increased risk for idiopathic thromboembolism compared with non-users. In younger women without heart disease this small increase in incidence (from 1/10 000 to 3/10 000 per year) appears acceptable, but in older women, particularly with established cardiovascular disease, both risks (from 23/10 000 to 62/10 000 per year) and benefits need to be weighed more carefully.

**Dosage**
Combination regimens, give either continuously (with a progestogen for 10–14 days each month) or for cycles of 3 weeks with a 7 day break, with a progestogen for last 10 days of estrogen.

Menopausal symptoms: Oral, 0.3–1.25 mg daily, use minimum dose to control symptoms.

Osteoporosis prevention: Oral, 0.625 mg daily.

**Patient counselling**
Tell your doctor immediately if you develop:
- symptoms of a blood clot (red, swollen or painful leg, difficulty in breathing, chest pain)
- changes in your breasts (skin changes, lump, nipple changes)
- changes in vaginal bleeding a few months after starting HRT (e.g. heavy or irregular bleeding, or bleeding after sex).

**Practice points**
- review need for treatment regularly (at least annually)
- withdraw HRT slowly, e.g. over 3–6 months, to minimise withdrawal symptoms
- choose vaginal preparations for women who only have urogenital symptoms
- irregular or atypical bleeding may indicate endometrial pathology and warrants further investigation
- HRT is not associated with improvement in quality of life (unrelated to relief of menopausal symptoms) and it is not effective for prevention of:
  - cardiovascular disease
  - dementia
  - anxiety or depression
- consider HRT for women without coronary heart disease (taking into account risks, e.g. cancer, VTE) to:
  - treat menopausal symptoms
  - prevent loss of bone mineral density and fractures in women at high risk of osteoporosis, when other treatments are inappropriate (however benefit does not appear to outweigh risks, even in these patients, unless vasomotor symptoms are very troublesome)
- consider need for progestogen carefully in women who have not had a hysterectomy; balance prevention of endometrial hyperplasia and reduced risk of endometrial carcinoma against the increased risk of breast
- women who dislike periods may benefit from:
  - reducing the estrogen dose or
  - using continuous progestogen or
  - using a progestogen course once every 3 months (produces less frequent withdrawal bleeds)

**Perimenopause**
- HRT does not provide contraceptive protection; conception can still occur in the perimenopause even though fertility is reduced.
- consider low dose oral contraceptives (in preference to HRT products) until the menopause occurs, then if still needed, change to HRT
- vasomotor symptoms may occur during the pill-free week for oral contraceptives; symptoms may be reduced by tricycling packs or using HRT doses of estrogen during this time.

**Products**
CONJUGATED EQUINE ESTROGENS VAGINAL CREAM 0.625 MG/GM 42.5 GM TUBE (ESTRIN®, PREMARIN®)

**DYDROGESTERONE**

**Indications**
HRT, as adjunct to estrogen (for combination products, see Estradiol).

Menstrual disorders, including amenorrhoea and period pain

Endometriosis.
Specific considerations
Renal impairment: Use cautiously in severe impairment, as progestogens may accumulate.
Hepatic impairment: Avoid use in severe impairment.
Pregnancy: Virilisation of female fetus if taken by the mother at or after 8 weeks post conception; no adverse effects before 8 weeks post conception; ADEC category D.
Breastfeeding: Safe to use.

Adverse effects
Common: menstrual irregularity (spotting, amenorrhoea, and oligomenorrhoea), nausea, abdominal bloating, weight gain, breast tenderness, virilisation, acne, libido changes, and mood changes.
Infrequent: depression, hypertension, breast cancer (HRT).
Rare: severe allergic reactions jaundice.

Dosage
HRT: 10 mg once daily for 12–14 days of the calendar month, or 5 mg daily continuously (with continuous estrogen).
If there is unacceptable withdrawal bleeding on 10 mg dose, use 20 mg daily for 12–14 days per cycle.
Amenorrhoea: 10 mg once or twice daily for days 11–25 of cycle (estrogen is needed for days 1–25).
Period pain: 10 mg twice daily for days 5–25 of cycle.
Endometriosis: 10 mg 2–3 times daily continuously, or from days 5–25 of cycle.

Practice points
- Dydrogesterone is less effective than other hormonal treatments for relief of pain caused by endometriosis.

Products
DYROGESTERONE TABS 10 MG (DUPHASTON®)

ESTRADIOL
Estrogen

Mode of action, Contraindications, Adverse effects, Patient counseling
Same as conjugated equine estrogens

Indications
Menopausal symptoms (e.g. hot flushes)
Prevention of osteoporosis, when non-estrogen treatment is inappropriate (tablets, patches); controversial,
Dysfunctional uterine bleeding, parenteral, seek specialist advice.
Primary or secondary amenorrhoea, parenteral, seek specialist advice.

Contraindications
Previous or active thromboembolic disorder
Unexplained uterine bleeding
Severe liver disease
Breast cancer or other oestrogen – dependent tumour.
Cerebrovascular or coronary artery disease

Specific considerations
Pregnancy: void use; ADEC category B1.
See conjugated equine estrogen.

Adverse effects
Common: nose bleeds, nasal irritation (nasal spray); skin irritation (patch)
These vary according to dose, regimen and patient characteristics.
Infrequent: breast cancer, premenstrual-like syndrome, dementia, migraine, stroke, venous thromboembolism,
pulmonary embolism, cardiovascular events, fluid retention, oedema, increased BP, endometrial hyperplasia, dry eye syndrome (combination HRT), acne, itch, nausea, increased triglycerides
Rare: gall stones, cholestatic jaundice, pancreatitis, glucose intolerance, galactorrhoea, visual changes, chloasma,
hypersensitivity (angioedema, urticaria), ovarian cancer, endometrial cancer, enlargement of uterine fibroids,
enlargement of hepatic haemangiomas
Breast cancer: The background incidence of breast cancer increases with age. Type of HRT and duration of use further increase the risk..

Studies have found:
- increase in breast cancer, seen within 3–4 years
- that, in contrast to previous studies, breast cancer was diagnosed at a more advanced stage (and was more likely to be fatal) for HRT users than for those taking placebo
- breast cancer risk was highest for those taking progesterone and oestrogen
• there was no evidence of a difference in breast cancer risk between sequential and continuous regimes, various routes of administration or different oestrogens or progestogens (risk with tibolone appears to be higher than for oestrogen alone and less than that of oestrogen and progestogen regimens)
• increased risk diminishes to that of never users after HRT has been stopped for 5 years.

**Endometrial cancer**
Oestrogen-only HRT is associated with an increased risk of endometrial hyperplasia and cancer. This risk is reduced by addition of a progestogen.

**Venous thromboembolism**
Women using HRT are likely to have a 2- to 4-fold increased risk for idiopathic thromboembolism compared with non-users. In younger women without heart disease this small increase in incidence (from 1/10 000 to 3/10 000 per year) appears acceptable, but in older women, particularly with established cardiovascular disease, both risk (increased from 23/10 000 to 62/10 000 per year) and benefits need to be weighed more carefully.

**Dosage**
Combination regimens, give either continuously (with a progestogen for 10–14 days each month) or for cycles of 3 weeks with a 7-day break, with a progestogen for last 10 days of oestrogen.

**Menopausal symptoms**
Oral, 1–4 mg each day, use minimum dose to control symptoms.
Patch, 1 patch (25–100 micrograms/24 hours) applied once a week (Climara®, Femtran®) or every 3–4 days (Dermestril®, Estraderm®, Estraderm MX®, Estradot®, Menorest®); individualise dose by changing the patch strength.
Gel, 0.5–1.5 g (oestradiol 0.5–1.5 mg) applied daily.
Implant, SC, 20–100 mg replaced as needed, usually every 4–8 months.
Nasal spray, 1 spray (150 micrograms) in each nostril daily (at the same time each day). Alter dose after 2–3 cycles according to response (1–4 sprays daily, give >3 sprays daily in divided doses).
Pessary, 1 pessary inserted into the vagina each day for 2 weeks, then reduce to twice a week.

**Osteoporosis prevention**
Oral, 1–2 mg daily.
Patch, 1 patch (25–100 micrograms/24 hours) applied once a week (Climara®, Femtran®) or every 3–4 days (Estraderm®, Estraderm MX®, Menorest®); individualise doses by changing the patch strength.

**Patient counselling**
Patch: apply to clean, dry skin on your lower abdomen or buttocks. When changing the patch, remove the old patch and apply a new one to a different place.
Tell your doctor immediately if you develop:
• symptoms of a blood clot (red, swollen or painful leg, difficulty in breathing or chest pain)
• changes in your breasts (skin changes, lump or nipple changes)
• changes in vaginal bleeding a few months after starting HRT (eg heavy or irregular bleeding, or bleeding after sex).

**Practice points**
• Ethinylestradiol (used in oral contraceptives) is 15–20 times more potent than estradiol when given orally
• Climen®, Progynova® and Primogyn Depot® contain estradiol valerate; all other products contain estradiol

**Products**
- ESTRADIOL 1-2 MG + DYdroGESTERON 5-10 MG (FEMOSTON®, FEMOSTON CONTI®)
- ESTRADIOL 2 MG + NorGestEROL 1 MG Tabs (PROGYLUTON®)
- ESTRADIOL 2 MG + NorTHESTERONE 1 MG Tabs (KLIOGEST®)
- ESTRADIOL VAGINAL Tabs 25 MCG (VAGIFEM®)

**TIBIOLONE**
**Mode of action**
Acts as an oestrogen on vagina, bone and thermoregulatory centres in brain. Has progestogenic and anti-oestrogenic effects on breast and endometrium. Androgenic effects include decrease in HDL, triglycerides and lipoprotein(a).

**Indications**
Menopausal symptoms, eg hot flushes

**Contraindications**
Pregnancy
Breast or genital tract cancer
Undiagnosed uterine bleeding
Severe liver disease
Cerebrovascular or coronary artery disease

Specific considerations
Previous or active thromboembolic disorder: no data available on magnitude of risk but a fibrinolytic effect has been shown.
Surgery: Consider temporarily stopping tibolone 4 weeks before abdominal or orthopaedic surgery to the lower limbs.
Pregnancy: Do not use; ADEC category D.

Adverse effects
Infrequent: dizziness, vertigo, rash, hypertrichosis, acne

Dosage
2.5 mg daily.

Practice points
- do not start tibolone until at least 12 months after last period to avoid increased irregular bleeding
- if switching from a sequential HRT preparation, start tibolone after the progestogen phase has been completed
- if switching from continuous, combined HRT, treatment can start at any time
- vaginal bleeding or spotting occurring soon after starting tibolone may be due to residual effects of endogenous or exogenous oestrogens; investigate bleeding occurring after >3 months of tibolone
- it is associated with an increased risk of breast cancer, greater than that of oestrogen-only regimens and less than that of combined (oestrogen with progestogen) regimens
- endometrial cancer risk is yet to be determined

Products
TIBIOLONE TABS 2.5 MG (LIVIAL®)

07.01.05 DRUGS FOR ENDOMETRIOSIS

DANAZOL
Mode of action
Inhibits gonadotrophin-releasing hormone (GnRH), suppresses menstruation, inhibits ovulation.

Indications
Endometriosis
Dysfunctional uterine bleeding
Benign fibrocystic breast disease
Prophylaxis of severe or life-threatening hereditary angioedema.

Contraindications
Undiagnosed abnormal vaginal bleeding
Previous or active thromboembolic disorders
Severe Hepatic impairment.
Acute porphyria
Pregnancy
Breastfeeding

Specific considerations
Cardiac disease, epilepsy, migraine: may be exacerbated due to fluid retention.
Diabetes: glucose tolerance may be impaired.
Renal impairment: Use with caution because of the risk of oedema; avoid use in severe impairment.
Hepatic impairment: Use with caution in mild-to-moderate impairment (contraindicated if severe).
Pregnancy: Contraindicated. If taken by the mother at or after 8 weeks post conception, danazol can cause virilisation of the female fetus. Before 8 weeks post conception it has no virilising effects. ADEC category D.
Women: Danazol may not inhibit ovulation in all women. Exclude pregnancy before starting danazol and advise use of effective method of non-hormonal contraception.

Adverse effects
Common: androgenic effects (occasionally not reversible) including acne, oily skin, weight gain, hirsutism and voice change, nausea, rash, hot flushes, oedema, hair loss, vaginal dryness, reversible menstrual disturbance, e.g. spotting, alteration of menstrual cycle, amenorrhoea.
Infrequent: effect on lipids (reduced HDL and increased LDL), impaired glucose tolerance, changes in libido.
Rare: thrombosis, cholestatic jaundice, benign hepatic adenoma (with long term use), elevation of liver enzymes
(e.g. ALP, transaminases), urticaria, rash, photosensitivity, erythema multiforme (including Stevens–Johnson syndrome), headache and visual disturbances (may indicate benign intracranial hypertension), splenic peliosis, leucopenia, thrombocytopenia, eosinophilia, erythrocytosis, polycythaemia.

**Dosage**

Endometriosis: 100–400 mg twice daily for 3–9 months.
Fibrocystic breast disease: 100 mg twice daily for 3–6 months.
Dysfunctional uterine bleeding: 200 mg daily for up to 6 months.
Hereditary angioedema: 100–300 mg twice daily, adjusted according to patient response.

**Counselling**

Stop taking this medicine and tell your doctor if you develop facial hair or your voice becomes deeper or hoarse.

**Practice points**

- stop danazol if signs of virilisation occur; they may be irreversible particularly with continued use.
- preliminary epidemiological evidence suggests that women taking danazol to treat endometriosis may have an increased risk of ovarian cancer.

**Products**

DANAZOL CAPS 200 MG (DANOL®)

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**TRIPTORELIN**

**Adverse Effects and Precautions**

Triptorelin and its analogues are generally well tolerated but may cause gastrointestinal adverse effects, usually nausea and abdominal pain or discomfort. There may be headache or lightheadedness, and an increase in menstrual bleeding. Continued therapy with Triptorelin analogues results in paradoxical suppression of the pituitary gonadal axis; in premenopausal women this may produce menopausal symptoms, including vaginal dryness, hot flushes, and loss of libido. If sufficiently prolonged the suppression of circulating oestrogens may lead to osteoporosis. In men, hot flushes and sexual dysfunction have occurred. Breast swelling and tenderness in men have been reported infrequently with gonadorelin analogues. Other adverse effects reportedly associated with gonadorelin analogue therapy, and presumably related to changes in the hormonal milieu, include mood changes, nervousness, palpitations, acne and dry skin, alterations in liver function tests and blood lipids, decreased glucose tolerance, and changes in scalp and body hair.

**Interactions**

Drugs affecting pituitary secretion of gonadotrophins may alter the response to Triptorelin or its analogues; other hormonal therapy and corticosteroids can affect the response. Spironolactone and levodopa can stimulate gonadotrophins while phenothiazines, dopamine antagonists, digoxin, and sex hormones can inhibit gonadotrophin secretion.

**Pharmacokinetics**

Triptorelin is rapidly absorbed following subcutaneous injection, with peak plasma concentrations achieved about 40 minutes after a dose. The biological half-life has been stated to be about 7.5 hours, although longer half-lives have been reported in patients with prostate cancer, and shorter half-lives in some groups of healthy subjects.

**Uses and Administration**

Triptorelin is an analogue of gonadorelin with similar properties. It is used for the suppression of gonadal sex hormone production in the treatment of malignant neoplasms of the prostate, in precocious puberty, and in the management of endometriosis, female infertility, and uterine fibroids. Triptorelin may be used as the base, acetate, diacetate, or embonate, although for preparations containing the acetate or diacetate it is not always obvious which has been used. Doses are usually given in terms of the base, and the following are each approximately equivalent to 1 mg of triptorelin:

- triptorelin acetate, 1.05 mg
- triptorelin diacetate, 1.09 mg
- triptorelin embonate, 1.30 mg

It is given as a daily subcutaneous injection, or as an intramuscular depot preparation lasting a month or longer. In the treatment of prostate cancer, a dose equivalent to triptorelin 3 or 3.75 mg is given intramuscularly as a depot preparation every 4 weeks; the first dose may be preceded by 100 micrograms daily for 7 days by subcutaneous injection. A longer-acting depot preparation that contains the equivalent of triptorelin 11.25 mg is given once every 12 to 13 weeks. An anti-androgen such as cyproterone acetate may be given for several days before beginning therapy with triptorelin and continued for about 3 weeks to avoid the risk of a disease flare.

Similar doses of the 3 or 3.75 mg depot preparations may be given for up to 6 months in the management of endometriosis or uterine fibroids, with treatment begun during the first 5 days of the menstrual cycle.
management of female infertility doses of 100 micrograms subcutaneously daily, with gonadotrophins, have been recommended from the second day of the menstrual cycle for about 10 to 12 days. In children with precocious puberty a dose equivalent to triptorelin 50 micrograms/kg from the 3-mg depot preparation may be given intramuscularly every 4 weeks. Alternatively, using the 3.75-mg preparation, doses of 1.875 mg for children weighing less than 20 kg, 2.5 mg for children of 20 to 30 kg, or 3.75 mg for children of more than 30 kg may be given; the first 3 doses should be given at 14-day intervals, with further doses given every 4 weeks.

**Delayed and precocious puberty.**
Gonadorelin analogues such as triptorelin are used in the management of central precocious puberty. They may also be effective in delayed puberty although they are most likely to be helpful where this is due to hypogonadism. Triptorelin has been used to differentiate gonadotrophin deficiency from constitutional delayed puberty.

**Disturbed behaviour.**
Combined therapy with triptorelin, which suppressed testosterone secretion by inhibiting the pituitary-gonadal axis, and supportive psychotherapy, has been tried in the treatment of men with paraphilias, a reduction in abnormal sexual thoughts and behaviours has been reported, although the study was uncontrolled.

**Endometriosis.**
Gonadorelin analogues are effective in the management of endometriosis, but the need for long-term therapy to prevent recurrence limits their value because of the risk of osteoporosis; ‘add-back’ therapy, with concomitant hormone replacement, can be used to prevent this.

**Growth retardation.**
As discussed, gonadorelin analogues have been given with growth hormone to short girls without growth hormone deficiency, in an attempt to delay puberty and bone maturation and thus maximise the final height achieved. However, there is some doubt about the extent of benefit, and in any case the concept of such treatment in children who are not clinically deficient in growth hormone is controversial, and some authorities do not consider it appropriate.

**Infertility.**
Gonadorelin analogues are used in the management of infertility related to hypogonadotrophic hypogonadism in both men and women.

**Products**

TRIPTORELIN VIALS 3.75 MG/VIAL (GONAPEPTYL®)

07.01.06 DRUGS TO DELAY LABOUR, SHORT ACTING BETA 2 AGONIST

**ATOSIBAN**

**Mode of action**
Atosiban is a peptide analogue of oxytocin but with oxytocin antagonist properties, which is licensed for the inhibition of uncomplicated premature labour between 24 and 33 weeks of gestation.

**Indications**
Uncomplicated premature labour

**Specific considerations**
Suspected cardiac disease (physician experienced in cardiology to assess), hypertension, hyperthyroidism, hypokalaemia (special risk with potassium-depleting diuretics), diabetes mellitus (closely monitor blood glucose during intravenous treatment), mild to moderate pre-eclampsia, monitor blood pressure and pulse rate (should not exceed 140 beats per minute), avoid over hydration (discontinue immediately and institute diuretic therapy if pulmonary oedema occurs): concomitant beta-blocker treatment: drugs likely to enhance sympathomimetic side effects or induce arrhythmias.

**Contra indications**
Cardiac disease, eclampsia and severe pre-eclampsia, intr-uterine infection, intra-uterine fetal death, antepartum haemorrhage, placenta prævia, cord compression

**Adverse effects**
Nausea, vomiting, flushing, sweating, tremor; hypokalaemia, tachycardia, palpitation, and hypotension
Uterine bleeding; pulmonary oedema; chest pain, arrhythmia; salivary gland enlargement

**Dosage**
An initial bolus dose equivalent to atosiban 6.75 mg is given by intravenous injection (as a solution containing 7.5 mg/mL) over one minute. This is immediately followed by a continuous infusion of 300 micrograms/minute for 3 hours, then 100 micrograms/minute for up to 45 hours, as a solution containing 750 micrograms/mL. The total duration of treatment should not exceed 48 hours, and the total dose should not exceed 330 mg.
**Products**
ATOSIBAN VIALS 7.5 MG/ML 5 ML VIAL (TRACTOCILE®)

**RITODRINE**

**Mode of action**
Ritodrine hydrochloride is a direct-acting sympathomimetic with predominantly beta-adrenergic activity and a selective action on beta2 receptors (a beta2 agonist). It decreases uterine contractility and is used to arrest premature labour.

**Indications**
Uncomplicated premature labour; asthma

**Specific considerations**
See under atosiban.

**Contra indications**
See under atosiban.

**Adverse effects**
Leucopenia or agranulocytosis, pulmonary oedema, retinopathy in premature infants when used for premature labour, myocardialischemia

**Dosage**
Ritodrine hydrochloride is usually given by intravenous infusion. Where possible this should be with the aid of a syringe pump, when the concentration should be 3 mg/mL, using glucose 5% as the diluent. A recommended initial rate of infusion is 50 micrograms/minute increased at intervals of 10 minutes by 50-microgram increments until there is evidence of patient response, which is usually at a rate of 150 to 350 micrograms/minute, the latter figure being the maximum recommended rate. If no syringe pump is available then the infusion may be made using a controlled infusion device to deliver a more dilute solution of 300 micrograms/mL, with glucose 5% being used once again as the diluent. The same dose is employed as with the syringe pump.

The maternal pulse should be monitored throughout the infusion and the rate adjusted to avoid a maternal heart rate of more than 140 beats per minute. A close watch should also be kept on the patient's state of hydration since fluid overload is considered to be a key risk factor for pulmonary oedema. The infusion should be continued for 12 to 48 hours after the contractions have stopped. Ritodrine hydrochloride may subsequently be given by mouth in an initial dose of 10 mg every 2 hours for 24 hours, starting 30 minutes before the end of the intravenous infusion. Thereafter, 10 to 20 mg may be given every 4 to 6 hours according to the patient's response. The total daily dose by mouth should not exceed 120 mg.

If intravenous infusion is inappropriate, 10 mg may be given intramuscularly every 3 to 8 hours and continued for 12 to 48 hours after the contractions have stopped.

**Products**
RITODRINE TABS 10 MG (AS HCL) (NOT REGISTERED)

**07.01.07 DRUGS IN PRE-ECLAMPSIA AND ECLAMPSIA**

**PRE-ECLAMPSIA AND ECLAMPSIA**
Pre-eclampsia is usually associated with proteinuria and hypertension, but can affect the liver, kidneys, clotting system, brain and placenta, and can lead to poor intrauterine growth and early delivery. It complicates 2–8% of pregnancies and can occur at any time in the second half of pregnancy. Although the outcome is often good, it may result in morbidity and mortality for the woman or baby.

Eclampsia (when a woman with pre-eclampsia has 1 or more seizures) is a rare but serious complication affecting 1 in 2000 deliveries in developed countries.

Magnesium sulfate is the drug of choice for treating eclampsia and also for pre-eclampsia: a study has shown it reduces the development of eclampsia in women with pre-eclampsia by about a half (compared to placebo) and also reduces maternal mortality. Outcome for the babies is unaffected

**MAGNESIUM SULFATE**

**Mode of action**
Unclear, has neuromuscular blocking action; effect in pre-eclampsia and eclampsia may be by relaxing smooth muscle including the vasculature, reducing cerebral ischaemia, or by blocking N-methyl-D-aspartate receptors in the brain, reducing calcium influx (which causes cell injury) into neurones.

**Indications**
Pre-eclampsia
Eclampsia
Hypomagnesaemia
Some cardiac arrhythmias including torsades de pointes and those associated with hypokalaemia

Contraindications
Heart block
Renal failure
Hypermagnesaemia

Specific considerations
Myasthenia gravis: magnesium interferes with neuromuscular transmission; possible marked increase in weakness, particularly of respiratory musculature; monitor closely.
Treatment with nifedipine: increases effects of magnesium sulfate and risk of hypotension; use cautiously, consider reducing magnesium sulfate dosage; monitor BP, deep tendon reflexes and respiratory function.
Renal impairment: Hypermagnesaemia may occur in severe impairment.
Hepatic impairment: Hypermagnesaemia may occur.
Breastfeeding: Unlikely to be of concern.

Adverse effects
Relate to hypermagnesaemia; important signs are loss of deep tendon reflexes followed by respiratory depression. More serious effects are hypotension, bradycardia, CNS depression, coma, circulatory collapse, cardiac arrest. Common: nausea, vomiting, flushing, thirst.

Dosage
Seek specialist advice for doses for patients with renal impairment and in indications other than pre-eclampsia or eclampsia
Dilute with sodium chloride 0.9% or glucose 5% according to local hospital protocol.
Pre-eclampsia (normal renal function): IV, 4 g given over 10–15 minutes followed by 1 g/hour for 24 hours.
Eclampsia (normal renal function)
Previous magnesium sulfate: IV, 2 g given over 10–15 minutes followed by 1 g/hour for 24 hours.
No previous magnesium sulfate: IV, 4 g given over 10–15 minutes followed by 1 g/hour for 24 hours.
Another 2 g dose (over 10–15 minutes) may be given if there is a further seizure.

Practice points
- before starting check that knee or other tendon reflex is present, respiratory rate is >16 respirations/minute and urine output is >100 mL during the previous 4 hours (or >25 mL/hour)
- monitor for clinical signs of hypermagnesaemia by checking urine output every hour, reflexes and respiration according to local protocol (Magpie trial suggests monitoring every 30 minutes); unnecessary to monitor plasma concentration in pre-eclampsia and eclampsia if renal function is normal
- be guided by local protocol if reflexes are slow, respiratory rate is reduced or urine output <100 mL in 4 hours; stop infusion if signs of toxicity develop; do not resume until signs are normal
- monitor plasma magnesium concentration regularly (e.g. every 6 hours) in reduced renal function (more often if oliguria develops) as well as checking for other signs of toxicity
- have calcium gluconate injection available in case of hypermagnesaemia requiring treatment.

Products
MAGNESIUM SULFATE AMPS 0.5  5 ML AMP (NOT REGISTERED)

07.01.08 DRUGS IN LABOUR

07.01.08.01 Prostaglandins

DINOPROSTONE
Also known as prostaglandin E₂

Mode of action
Contract or relax smooth muscle in blood vessels, bronchi, uterus and GIT. Inhibit gastric acid secretion. Have effects on platelet aggregation, the endocrine system and metabolic processes.

Indications
Induction or augmentation of labour in women with an unfavourable cervix at or near term
**Contraindications**
Ruptured membranes (pessary).
Fetal distress
Malpresentation
Cephalopelvic disproportion
Previous pregnancies (5 or more for the gel, 3 or more for the pessary)
Unexplained vaginal discharge and/or abnormal uterine bleeding during the current pregnancy
Multiple pregnancy
Untreated pelvic infection
Previous caesarean section or major uterine surgery

**Specific considerations**
Ruptured membranes: theoretical risk of increased absorption with possible increase in toxicity (gel).
Epilepsy: use with caution.
Bishop score of 8 or more: use with caution.
Pregnancy: Idiosyncratic sensitivity of the uterus has resulted in fetal anoxia; ADEC category C.
Asthma, COPD: may cause bronchospasm.
Active cardiac disease: bradycardia and decreases in BP may worsen, exacerbating angina or leading to cardiovascular collapse.
Raised intraocular pressure, glaucoma: use with caution.
Treatment with other drugs that augment uterine contraction (e.g. oxytocin, ergometrine): increase risk of uterine rupture; avoid combination (use of prostaglandin to induce labour may be followed by oxytocin infusion).
Hepatic impairment: Avoid use in severe impairment.

**Adverse effects**
Common: nausea, vomiting, diarrhoea, back pain, transient hypertension or hypotension, bronchoconstriction, headache, epigastric pain, vasovagal symptoms, blurred vision, facial flush, fever, altered fetal heart rate, uterine hypercontractility and hypertonus.
Rare: uterine rupture.

**Dosage**
Gel: 1–2 mg of vaginal gel into posterior fornix. Dose may be repeated after 6 hours, with a maximum dose of 4 mg over 6 hours.
Pessary: 1 pessary placed transversely into posterior fornix; 4 mg is released from the pessary over 12 hours; a second dose is not recommended.

**Administration instructions**
The woman should lie down for 30 minutes after insertion.
Pessary: Leave sufficient tape outside the vagina so that the pessary can be removed.

**Practice points**
- monitor uterine activity and fetal heart rate regularly after administration
- remove pessary when:
  - membranes rupture
  - regular, painful contractions begin
  - adverse effects or maternal or fetal condition warrants it
  - after 12 hours if insufficient effect
- these products are for use only where facilities for emergency obstetric and gynaecological care are available

**Products**
DINOPROSTONE VAGINAL TABS 3 MG (PROSTIN E2®)

**MISOPROSTOL**

**Mode of action**
Contract or relax smooth muscle in blood vessels, bronchi, uterus and GIT. Inhibit gastric acid secretion. Have effects on platelet aggregation, the endocrine system and metabolic processes.

**Indications**
Termination of second trimester pregnancy
Second and third trimester stillbirth

**Contraindications**
Untreated pelvic infection
Previous caesarean section or major uterine surgery

Specific considerations
Asthma, COPD: may cause bronchospasm.
Active cardiac disease: bradycardia and decreases in BP may worsen, exacerbating angina or leading to cardiovascular collapse.
Raised intraocular pressure, glaucoma: use with caution.
Treatment with other drugs that augment uterine contraction (e.g. oxytocin, ergometrine): increase risk of uterine rupture; avoid combination (use of prostaglandin to induce labour may be followed by oxytocin infusion).
Hepatic impairment: Avoid use in severe impairment.

Adverse effects
Common: nausea, vomiting, diarrhoea, back pain, transient hypertension or hypotension, bronchoconstriction, headache, epigastric pain, vasovagal symptoms, blurred vision, facial flush, fever, altered fetal heart rate, uterine hypercontractility and hypertonus.
Rare: uterine rupture.

Dosage
Termination of second trimester pregnancy: 200 micrograms (1 tablet) inserted into the vagina every 6 hours for 2 doses, then 200–400 micrograms every 6 hours for a total of 4 doses. Review progress each 24 hours. Repeat course if required.
Second trimester stillbirth: 200 micrograms (1 tablet) inserted into the vagina every 12 hours. Higher doses have also been used.
Third trimester stillbirth: 100 micrograms (half a 200 microgram tablet) inserted into the vagina every 12 hours.

Practice points
- misoprostol can also be used in sequence with other agents, eg oxytocin
- the American FDA has sanctioned the use of misoprostol for a number of indications in pregnancy.
- may be an alternative for prevention of postpartum haemorrhage when other agents are ineffective or unavailable but should not be used routinely (give 400–600 micrograms orally or rectally immediately after delivery)
- these products are for use only where facilities for emergency obstetric and gynaecological care are available

Products
MISOPROSTOL TABS 200 MCG (CYTOTEC®)

07.01.08.02 Others

ERGOMETRINE
Ergot alkaloid
Mode of action
Stimulates contraction of uterine smooth muscle
Indications
Prevention or treatment of postpartum haemorrhage
Contraindications
Pregnancy (may use after second stage of labour).
Pre-eclampsia
Severe fibroids
Severe peripheral vascular disease
Specific considerations
Multiple pregnancy: ergometrine may result in death of second fetus due to excessive uterine contraction.
Ischaemic heart disease, peripheral vascular disease, hypertension: may be exacerbated by vasoconstriction.
Acute Porphyria: may cause an attack.
Hepatic impairment: Avoid use in severe impairment.
Pregnancy: Avoid use; induces uterine contraction and may cause premature or hypertonic labour; ADEC category C.
Adverse effects
Usually well tolerated. Adverse effects are more common with IV route.
Common: nausea and vomiting.
Infrequent: hypertension, abdominal pain, headache.
Rare: MI, cerebral infarction, gangrene, pulmonary oedema.

**Dosage**

**Prevention of postpartum haemorrhage**
IM, 200 micrograms following delivery of the placenta

**Treatment of postpartum haemorrhage**
IV, 25–50 micrograms; dose may be repeated after 2–3 minutes.
IM, 250 micrograms

**Practice points**
- not appropriate for induction of labour

**Products**

ERGOMETRINE AMPS 200 MCG/AMP (AS HYDROGEN MALEATE) 1 ML AMP (DEMERGIN®, METHERGIN®, METHYLERGOMETRINE MALEATE®)
ERGOMETRIN E TABS 125 MCG (AS HYDROGEN MALEATE) (METHERGIN®)

**OXYTOCIN**

Synthetic pituitary hormone

**Mode of action**
Stimulates uterine muscle contraction.

**Indications**

Induction and augmentation of labour
Active management of third stage of labour
Prevention and treatment of postpartum haemorrhage

**Contraindications**

When vaginal delivery is contraindicated (cephalopelvic disproportion, placenta praevia, fetal distress, prolapsed cord, malpresentation, vasa previa, placental abruption).

**Specific considerations**

Previous uterine surgery, multiple pregnancy: increased risk of uterine rupture.
Prior caesarean section: monitor carefully for evidence of scar dehiscence.
Cardiovascular disease: avoid over hydration; monitor cardiovascular status closely.
Fetal death in utero or meconium-stained amniotic fluid: avoid tumultuous labour (may cause amniotic fluid embolism).
Concomitant prostaglandins: monitor carefully; effects of oxytocin enhanced.
Pregnancy: ADEC category A.

**Adverse effects**

Infrequent: nausea, vomiting.
Rare: arrhythmias, water intoxication, hyponatraemia and cerebral oedema with high doses, anaphylactoid reaction, severe (tetanic) uterine contraction leading to fetal hypoxia and death.

**Dosage**

**Induction after rupture of membranes and augmentation of labour**
IV infusion, 1–6 milliunits/minute, increased at intervals of >30 minutes to a maximum of 48 milliunits/minute. (1000 milliunits = 1 unit.)
Monitor fetal heart rate and uterine motility so that dose can be adjusted according to response.
Active management of third stage of labour
IM/IV, 10 units given with or after delivery of the shoulder

**Treatment of postpartum haemorrhage**
IM, 10 units or IV 5–10 units. In severe cases may be followed by an IV infusion (see local protocols).
Combination with ergometrine
For additional information see Ergometrine
Active management of third stage of labour
IM, 500 micrograms ergometrine with oxytocin 5 units (give as 1 mL Syntometrine®), with or after delivery of the shoulder.
Prevention or treatment of postpartum haemorrhage
IM, 500 micrograms ergometrine with oxytocin 5 units (give as 1 mL Syntometrine®), following expulsion of the placenta, or when bleeding occurs. Dose may be repeated after 2 hours.
Administration instructions
For IV infusion a suggested dilution is 10 units oxytocin in 1 L Hartmann's solution to give a strength of 10 milliunits/mL.

Practice points
- when used for induction and augmentation of labour continuous electronic fetal monitoring is required
- combination with ergometrine for active management of third stage of labour may increase likelihood of adverse effects and has little advantage over oxytocin alone, see Drugs in labour

Products
OXYSYTOCIN 5 IU+ERGOMETRINE 0.5 MG/ML AMPS 1 ML AMP (NOT REGISTERED)
OXYSYTOCIN AMPS 5 IU/AMP 1 ML AMP (SYNTOCINON®)
OXYSYTOCIN AMPS 10 IU/AMP 1 ML AMP (NOT REGISTERED)

07.01.09 DRUGS FOR VAGINAL INFECTIONS

ISOCONAZOLE (VAGINAL)
Mode of action
Impair biosynthesis of ergosterol for cytoplasmic membrane, inhibiting fungal growth; fungistatic

Indications
Vulvovaginitis

Dosage
For vaginal infections it is usually given as pessaries in a single dose of 600 mg or 300 mg daily for 3 days, or as a 1% vaginal cream daily for 7 days. For skin infections a 2% cream or other topical formulation has been used.

Products
ISOCONAZOLE VAGINAL CREAM 0.01 % (AS NITRATE) 40 GM TUB (AZONIT®)

MICONAZOLE (VAGINAL)
Mode of action
Impair biosynthesis of ergosterol for cytoplasmic membrane, inhibiting fungal growth; fungistatic.

Indications
Vulvovaginal candidiasis

Specific considerations
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Safe to use.

Adverse effects
Topical imidazoles are generally well tolerated.
Infrequent: burning, stinging, itch, erythema.
Rare: allergic reactions.

Dosage
Vaginal cream, insert 1 applicatorful into the vagina once daily at bedtime for 7 days.
Pessary, insert 1 pessary into the vagina daily at bedtime for 7 days

Patient counseling
It is important to finish the full treatment, even if your symptoms have gone. This medicine may damage contraceptive diaphragms and condoms; do not rely on these methods while using this medicine.

Practice points
- Intractable candidiasis may be the presenting symptom of undiagnosed diabetes; appropriate urine and blood tests may be indicated in patients unresponsive to treatment.

Products
MICONAZOLE VAGINAL CREAM 2 % (AS NITRATE) 78 GM TUB (GYNO-DAKTARIN®, GYNO-MECOZOL®)

MICONAZOLE VAGINAL OVULES 400 MG (AS NITRATE) (GYNO-CANDIZOL®, GYNO-MECOZOL®, MICOVER®, MYCOHEAL®)
POLICRESULEN
Policresulin is an antiseptic used in infections of mucous membranes.

Products
POLICRESULIN VAGINAL OVULES 90 MG (ALBOTHYL®)

07.01.11 ASORTED
ETAMSYLATE
Mode of action
Etamsylate is a haemostatic that appears to maintain the stability of the capillary wall and correct abnormal platelet adhesion. It is given for the prophylaxis and control of haemorrhages from small blood vessels.
Indications
Short term blood loss in menorrhagia
Contraindications
Porphyria
Adverse effects
Nausea, headache, and skin rash have occurred after administration of etamsylate. Transient hypotension has been reported following intravenous injection.
Dosage
500 mg 4 times daily during menstruation
Products
ETAMSYLATE TABS 250 MG (DICYNON®)

GLYCIN
Use and Administration
Glycine is the simplest of the amino acids. It is used as a dietary supplement.
Indications
Sterile solutions of glycine 1.5% in water, which are hypotonic and non-conductive, are used as urogenital irrigation solutions during certain surgical procedures, particularly transurethral resection of the prostate.
Contraindications
Glycine irrigation is contra-indicated in anuric patients.
Specific considerations
Glycine irrigation should be used cautiously in patients with hepatic impairment since any absorption and consequent metabolism may cause hyperammonaemia. The possible effects on fluid and electrolyte balance warrant cautious use in patients with cardiopulmonary or renal dysfunction
Adverse effects
Systemic absorption of glycine irrigation solutions can lead to disturbances of fluid and electrolyte balance and cardiovascular and pulmonary disorders.
Products
GLYCIN IRRIGATION SOLUTION (NOT REGISTERED)

LIDOCAINE (LOCAL)
Mode of action
Lidocaine is a local anaesthetic of the amide type.
Indications
It is a useful topical application in urethral pain or to relieve the discomfort of catheterization.
It is used for infiltration anaesthesia and regional nerve block
Adverse effects
As for Local Anaesthetics in general may have systemic adverse effects as a result of the raised plasma concentrations which occur when the rate of absorption into the circulation exceeds the rate of breakdown or when a vasoconstrictor is added to the preparation.
Allergy: hypersensitivity reactions and anaphylaxis.
Cardiovascular system: hypotension, bradycardia, and cardiac arrest may occur if massive systemic absorption occurs.
Central nervous system: agitation, euphoria, respiratory depression, and convulsions.

**Dosage**
Lidocaine ointment is used for anaesthesia of skin and mucous membranes with a maximum recommended total dose of 20 g of 5% ointment (equivalent to 1 g of lidocaine base) in 24 hours.

**Products**
LIDOCAINE OINTMENT 5 % (AS HCL)  35 GM TUBE (LIDOCAINE®, XYLOCAINE®)

**MECLOZINE+PYRIDOXINE**

**Mode of action**
Meclozine hydrochloride, a piperazine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties.

**Indications**
It is mainly used for its antiemetic action, which may last for up to 24 hours. Meclozine hydrochloride is used in the prevention and treatment of nausea and vomiting associated with a variety of conditions including motion sickness and for the symptomatic treatment of vertigo caused by Ménière's disease and other vestibular disorders. Meclozine hydrochloride has also been used for the symptomatic relief of hypersensitivity reactions and pruritic skin disorders.

**Contraindications**
Hypersensitivity to meclizine hydrochloride, narrow-angle glaucoma

**Specific considerations**
Pregnancy: ADEC category B. Safety of drug in children under 12 years has not been established. Use meclizine with caution in patient with asthma and prostatic enlargement.

**Adverse effects**
Central nervous system: drowsiness.
Gastrointestinal: dry mouth.
Ophthalmic: blurred vision.

**Dosage**
The usual dose of meclozine hydrochloride for motion sickness is 25 to 50 mg by mouth taken about one hour before traveling and repeated every 24 hours if necessary; up to 100 mg daily in divided doses has been given for the treatment of vertigo and vestibular disorders.

**Patient counseling**
- take after meals
- do not discontinue drug abruptly
- notify physician if adverse GI effects, fever, or heart intolerance occurs
- may cause drowsiness
- avoid alcohol
- adequate fluid and exercise may help constipation.

**Products**
MECLOZINE 25 MG+PYRIDOXINE 50 MG TABS (AS HCL) (NAVIDOXINE®, VOMINORE®)

07.02 GENITOURINARY DRUGS
07.02.01 ANTICHOLINERGICS

**FLAVOXATE**

**Mode of action**
Flavoxate hydrochloride is described as a smooth muscle relaxant but it also has antimuscarinic effects; it is a tertiary amine.

**Indications**
Urinary frequency and incontinence, dysuria, urgency
Bladder spasms due to catheterization

**Contraindications**
Gastrointestinal haemorrhage

**Specific considerations**
Pregnancy: avoid unless no safer alternative.
Breast-feeding: use with caution, no information available
Safety of drug in children under 12 years has not been established (not recommended).

**Adverse effects**
As for Atropine Sulfate, Ocular effects, including increased intra-ocular pressure, are occasionally troublesome.
Other adverse effects include sedation or fatigue, vertigo, and hypersensitivity reactions. Leucopenia or eosinophilia has been reported rarely.

**Dosage**
A usual dose is 200 mg by mouth three times daily.

**Products**
FLAVOXATE TABS 200 MG (AS HCL) (URISPAS®)

**OXYBUTYNNIN**

**Indications**
Urinary urge incontinence, including paediatric neurogenic urge incontinence

**Specific considerations**
Pregnancy: Little experience; ADEC category B1.
Breastfeeding: Unlikely to be of concern.

**Adverse effects**
Common: facial flushing (more common in children).
Rare: cognitive dysfunction (confusion, hallucinations, anxiety, paranoia).

**Dosage**
Usual range: 2.5–5 mg 2–3 times daily.
Maximum: 20 mg daily.
Elderly: Start with 2.5 mg at night and increase slowly if necessary.
Child: ≤5 years, 0.2 mg/kg 2–3 times daily. >5 years, 2.5–5 mg 2–3 times daily.

**Products**
OXYBUTYNIN TABS 5 MG (AS HCL) (DITROPAN®)

**TOLTERODINE**

**Indications**
Urinary urge incontinence

**Specific considerations**
Renal impairment: reduce dose if creatinine clearance <30mL/minute
Hepatic impairment: Reduce dose.
Pregnancy: No human data; avoid use; ADEC category B3.
Breastfeeding: No human data.

**Adverse effects**
Common: facial flushing (more common in children).
Rare: anorexia, cognitive dysfunction (confusion, hallucinations, anxiety, paranoia).

**Dosage**
2 mg twice daily; reduce to 1 mg twice daily if necessary to minimise adverse effects.
Hepatic impairment: 1 mg twice daily.

**Products**
TOLTERODINE TABS 2 MG (AS TARTRATE) (DETRUSITOL®)

**07.02.02 DRUGS FOR BENIGN HYPERPLASIA AND PROSTATITIS, SELECTIVE ALPHA BLOCKERS**

**DOXAZOCIN**

**Mode of action**
Doxazocin has post-synaptic alpha-blocking and vasodilator properties it relax smooth muscle in the bladder neck and prostate, decreasing resistance to urinary flow.

**Indications**
Hypertension
Benign prostatic hyperplasia
Specific considerations
Pregnancy: no evidence of teratogenicity, manufacturer advises use only when potential benefit outweigh risk.
Lactation: Doxazocin accumulates in milk, manufacturer advises to avoid.

Adverse effects
Common: postural hypotension; dizziness, vertigo, headache, fatigue, asthenia, oedema, sleep disturbance, nausea, rhinitis.
Infrequent: abdominal discomfort, diarrhea, vomiting, agitation, tremor, rash, pruritus.
Rare: blurred vision, epistaxis, haematuria, thrombocytopenia, purpura, leucopenia, hepatitis, jaundice, cholestasis, and urinary incontinence.

Dosage
Hypertension: 1mg daily, increased after 1-2 weeks to 2 mg once daily, and thereafter to 4 mg once daily, if necessary: max. 16 mg daily.
Benign prostatic hyperplasia the usual maintenance dose is 2 to 4 mg daily; doses of 8 mg daily should not be exceeded.

Patient counseling
Dizziness on standing may occur; get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy.

Practice points
- first dose hypotension is common with the selective alpha-blockers; it is most serious in the elderly and in patients with fluid depletion or who are taking diuretics
- minimise first dose hypotension by giving the first dose at bedtime
- people on other antihypertensive treatment require close supervision because of possible additive hypertensive effects,
- if treatment is interrupted for several days, restart and titrate dosage as if starting for the first time
- dose must be adjusted according to individual response
- stop if there is no benefit after 4–6 weeks of maximal treatment.

Products
DOXAZOSIN TABS 1 MG (AS MESYLATE) (ALPHAPRESS®, CARDOX®, CARDURA®, CURCARD®, MAGUROL®)
DOXAZOSIN TABS 4 MG (AS MESYLATE) (ALPHAPRESS®, CARDOX®, CARDURA®, CURCARD®, MAGUROL®)

TAMSULOSIN
Mode of action
Relax smooth muscle in the bladder neck and prostate, decreasing resistance to urinary flow
Indications
Symptom relief in BPH
Contraindications
Allergy to tamsulosin
Adverse effects
Common: retrograde ejaculation
Rare: hypersensitivity reactions, angioedema, urticaria
Dosage
400 micrograms once daily, in the morning.
Patient counseling
Swallow capsule whole, with or after food.
Dizziness on standing may occur especially when starting treatment or when the dose is increased. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy. Take the first dose at bedtime, but be careful if you get up during the night as you may feel dizzy.
This medicine may cause drowsiness or dizziness; do not drive or operate machinery if affected.
Practice points
- first dose hypotension is common with the selective alpha-blockers; it is most serious in the elderly and in patients with fluid depletion or who are taking diuretics
- people on other antihypertensive treatment require close supervision because of possible additive hypertensive effects
- if treatment is interrupted for several days, restart and titrate dosage as if starting for the first time
• dose must be adjusted according to individual response
• stop if there is no benefit after 4–6 weeks of maximal treatment.

Products
TAMSULOSIN CAPS 0.4 MG (AS HCL) (OMNIC®)

TERAZOSIN
Mode of action
Relax smooth muscle in the bladder neck and prostate, decreasing resistance to urinary flow
Indications
Management of hypertension and BPH to relief symptoms of urinary obstruction.
Adverse effects
Weight gain, paraesthesia, dyspnoea, thrombocytopenia, nervousness, decreased libido, back pain and pain in extremities.
Dosage
Initially 1 mg daily for 7 days, then 2 mg daily for 7 days; then increase dose according to clinical response up to 5–10 mg each morning.
Patient counseling
See under doxazosin.

Products
TERAZOSIN TABS 2 MG (AS HCL) (ITRIN®)
TERAZOSIN TABS 5 MG (AS HCL) (ITRIN®,TERASTAT®)

07.02.03 DRUGS FOR ERECTILE DYSFUNCTION
ALPROSTADIL
Also known as prostaglandin E.
Mode of action
Dilates cavernosal arteries. Relaxes smooth muscle of corpus cavernosum and spongiosum
Indications
Erectile dysfunction, treatment and diagnostic testing
Contraindications
Conditions predisposing to priapism (sickle cell anaemia, myeloma, leukaemia)
Penile fibrosis.
Penile implant
Men for whom sexual intercourse is inadvisable (e.g. those with cardiovascular disease).
Specific considerations
Anticoagulants or coagulopathies: increases risk of urethral bleeding or bleeding at injection site.
HIV, hepatitis B or C: bleeding at injection site may increase risk of transmission of disease to partner.
Anatomical deformation of penis: may require urological assessment; painful erections are more likely to occur and fibrosis may result from treatment.
Adverse effects
Common: penile pain, erection lasting 4–6 hours, fibrotic change (may be more likely with increasing duration of use)
Infrequent: fainting, painful erection, erection lasting >6 hours, testicular pain, bruising, injection site reactions, hypotension, dizziness.
Dosage
Give by intracavernosal injection.
Usual range, 10–20 micrograms; maximum dose 60 micrograms. Use no more than 1 injection in 24 hours; may be used up to 3 times a week.
Erectile dysfunction of predominantly psychogenic or unknown aetiology
Initially, 2.5 micrograms; increase in increments of 2.5 micrograms according to response.
Erectile dysfunction of organic origin, including vasculopathy
Initially, 5 micrograms; increase in increments of 5 micrograms according to response.
Adjunct in diagnosis of impotence
Initially, 2.5 micrograms; increase in increments of 2.5 micrograms.
Administration instructions
See pack insert and material available from manufacturer. The first dose should be given by a medical practitioner and the procedure for self-administration explained.

**Patient counselling**
Tell your doctor if you have increased or new pain in your penis, or if you notice nodules or bending in the penile shaft.

Store below 25°C; once solution is made use it as soon as possible (but you can keep it in the fridge for up to 24 hours if necessary).

**Practice points**
- check on dosage being used and possible development of fibrosis at regular follow-up visits
- stop treatment if fibrosis develops

**Products**
ALPROSTADIL AMPS OR VIAL 20 MCG/AMP OR VIAL (CAVERJECT®, PROSTAVASIN®)

**PAPAVERINE**

**Mode of action**
Relaxation of all vascular components of the penile erectile system

**Indications**
Erectile dysfunction

**Contraindications**
Conditions predisposing to priapism (sickle cell anaemia, myeloma, leukaemia)
Penile fibrosis
Penile implant
Men for whom sexual intercourse is inadvisable (e.g. complete atrioventricular block)

**Specific considerations**
HIV, hepatitis B or C: bleeding at injection site may increase risk of transmission of disease to partner.
Anticoagulants or coagulopathies: increases risk of urethral bleeding or bleeding at injection site.
Anatomical deformation of penis, e.g. Peyronie’s disease: may require urological assessment; painful erections are more likely to occur.

**Hepatic impairment**
Avoid use in severe impairment

**Adverse effects**
Systemic effects are rare.
Loss of penile sensation and difficulty in obtaining an erection may occur.
Common: pain and bruising on injection, priapism, penile fibrosis (related to injection volume >1 mL and minimal if used with alprostadil)
Infrequent: penile pain
Rare: dizziness, tachycardia, hepatitis, allergy

**Dosage**
Intracavernosal injection, initially 5–15 mg; adjust up to 60 mg according to response. Use the lowest effective dose, which may be as low as 2.5 mg.
Usual range: 30–60 mg.

**Administration instructions**
See material available from manufacturer. The first dose should be given by a medical practitioner and the procedure for self-administration explained.

**Patient counselling**
Be careful when getting up from sitting or lying as this injection may make you feel dizzy.
Tell your doctor if you have increased or new pain in your penis, or if you notice nodules or bending in the penile shaft.

**Practice points**
- check on dosage being used and possible development of fibrosis at regular follow-up visits
- stop treatment if fibrosis develops
- tolerance may develop, requiring an increase in dosage.
Products
PAPAYERINE AMPS 40 MG/AMP (NOT REGISTERED)
### Table 07–01 Comparison of emergency contraceptive methods

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Frequency of unintended pregnancy*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel tablets</td>
<td></td>
<td>• no absolute contraindications • convenient, well tolerated • vomiting affects 1–5%</td>
</tr>
<tr>
<td>1.5 mg single dose (as 2x750 mcg tablets or 50x30 mcg tablets)</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>COC (Yuzpe)</td>
<td></td>
<td>• no absolute contraindications • no longer recommended • poor efficacy; poorly tolerated • vomiting affects 20%</td>
</tr>
<tr>
<td>2 doses of 4 tablets containing 30 mcg ethinyloestradiol and 150 mcg levonorgestrel, 12 hours apart</td>
<td>&lt;4%</td>
<td></td>
</tr>
<tr>
<td>Copper IUD</td>
<td></td>
<td>• inserted and removed by doctor • several contraindications • not affected by drug interactions or GI problems • option of long term protection</td>
</tr>
<tr>
<td>1 device, remove at end of cycle or retain for ongoing contraception</td>
<td>&lt;0.1%</td>
<td></td>
</tr>
</tbody>
</table>

*Risk of pregnancy after unprotected sex varies during the menstrual cycle from 2–4% to 20–30%.

### Table 07–02 Comparison of contraceptive methods

<table>
<thead>
<tr>
<th>Failure rate*</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptives</td>
<td></td>
<td>• efficacy affected by certain drugs, vomiting and severe diarrhoea</td>
</tr>
<tr>
<td>0.2–3</td>
<td>regular, lighter, less painful periods • improve acne and menstrual disorders • reduce risk of PID, anaemia and ovarian and endometrial cancer</td>
<td>• need to be taken each day • may cause spotting between periods, nausea, vomiting, breast enlargement and tenderness, headache, fluid retention, weight changes, increase in BP, mood changes, VTE (rare) • increase risk of MI and stroke in smokers &gt;35 years or those with hypertension</td>
</tr>
<tr>
<td>Progestogen-only contraceptives</td>
<td>Oral</td>
<td></td>
</tr>
</tbody>
</table>
• useful when COC is contraindicated/less appropriate (eg breastfeeding, migraine, history of DVT, smokers >35 years) or not tolerated
• needs to be taken at the same time every day (within 3 hours)
• efficacy affected by certain drugs, vomiting and severe diarrhoea
• may cause amenorrhoea, irregular bleeding, breast tenderness, acne

**Medroxyprogesterone IM depot**

- no daily tablets
- provides prolonged contraception (12 weeks)

**Etonogestrel implant**

- readily reversible
- no daily tablets
- provides long term contraception (3 years)

**Levonorgestrel IUD**

- almost immediately reversible
- no daily tablets
- provides long term contraception (5 years)

**Barrier methods**

- no hormonal adverse effects
- condoms are easy to use, readily available, protect against STI including HIV
- **condoms** may rupture or split or slip off
- **diaphragm** is initially fitted by nurse or doctor, woman needs to be taught to place it correctly (some find this difficult)
- latex may rarely cause allergic reactions (polyurethane condoms are an alternative; more expensive)

**Copper-releasing IUD**

- no hormonal adverse effects
- efficacy unaffected by enzyme-inducing drugs or GI problems
- doctor inserts and removes
- may cause heavy periods, period pain, increases risk of pelvic infection (for
eg vomiting
- long term quickly reversible contraception (5 or 8 years depending upon brand); may be used for emergency contraception
- 3 weeks after insertion, device may be expelled (especially in first year)

**Spermicides**

- may increase effectiveness of barrier methods
- not reliable if used alone, more effective methods are available
- messy
- may cause skin/mucosal irritation (mild), allergic dermatitis (rare), may increase risk of STI

6–26

* per 100 woman years

**Table 07–03 Management of HRT adverse effects**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>heavy withdrawal bleeds</td>
<td>reduce estrogen</td>
</tr>
<tr>
<td>absent withdrawal bleed</td>
<td>reassure; no change in treatment necessary</td>
</tr>
<tr>
<td>bleeding during progestogen therapy</td>
<td>increase progestogen dose</td>
</tr>
<tr>
<td>breast tenderness</td>
<td>reduce estrogen then slowly increase dose if necessary after 3 months</td>
</tr>
<tr>
<td>nausea</td>
<td>take tablets with food or at night or try a patch or gel</td>
</tr>
<tr>
<td>persistent vasomotor symptoms</td>
<td>increase estrogen</td>
</tr>
<tr>
<td>persistent vulvovaginal symptoms</td>
<td>add topical estrogen</td>
</tr>
<tr>
<td>premenstrual symptoms during progestogen therapy</td>
<td>reduce progestogen dose or try a different progestogen</td>
</tr>
</tbody>
</table>

**Table 07–04 Comparison of drug choices for ovulatory DUB**

<table>
<thead>
<tr>
<th>Reduction of menstrual blood loss</th>
<th>Contraception provided?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–50%</td>
<td>no</td>
<td>• taken only during periods&lt;br&gt;• improves period pain, headache and diarrhoea</td>
</tr>
<tr>
<td><strong>Tranexamic acid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–60%</td>
<td>no</td>
<td>• taken only during periods</td>
</tr>
<tr>
<td><strong>Combined oral contraceptives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>yes</td>
<td>• improves period pain</td>
</tr>
<tr>
<td>Progestogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel IUD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 90%; amenorrhoea in 20–50% of women after 1 year | yes | • improves period pain  
• no need to take tablets  
• can be used long term (replace every 5 years) |
| Oral |  |
| 90% | no | • taken on days 5–25  
• treatment poorly accepted compared to levonorgestrel IUD  
• disrupts menstrual cycle |
| Medroxyprogesterone IM depot |  |
| unknown; amenorrhoea in 50% of women after 1 year | yes | • no need to take tablets  
• disrupts menstrual cycle; spotting and light bleeding in 40–50%, heavy bleeding in 1–2% |
| Danazol |  |
| up to 80% (dose dependent) | yes; but additional non-hormonal contraception also required | • poorly tolerated  
• treatment duration limited to 6 months |
| GnRH analogues |  |
| >90% | yes; but additional non-hormonal contraception also required | • improves period pain  
• limited by adverse effects  
• treatment duration limited to 6 months |
CHAPTER 08 IMMUNOMODULATORS AND ANTINEOPLASTICS

08.01 IMMUNOSUPPRESSANTS

IMMUNOSUPPRESSION

Rationale for drug use
Prevent organ rejection and reverse acute rejection in organ transplantation.
Prevent and treat graft-versus-host disease.
Minimise destruction of affected tissues in autoimmune and inflammatory diseases.

Before starting treatment
Ensure the patient does not have an uncontrolled infection, or recent exposure to shingles, chickenpox or measles without prior immunity.
Vaccinate potential transplant patients well before transplantation whenever possible. Check for exposure to Epstein–Barr virus, hepatitis B and hepatitis C, CMV, HIV.
Exclude malignancy before immunosuppression.
Perform dental procedures before immunosuppression if possible, to minimise risk of infection.
Measure baseline markers of disease activity in autoimmune disorders
Ensure patient is not pregnant and is using effective contraception where the agent of choice is teratogenic.
Assess patient's ability to comply with medication regimens and ensure understanding of the potential need for emergency medical assistance if infection occurs.

When to start treatment
Immediately before, or as soon as possible after, transplantation depending on treatment regimen.
Treatment may be started several days before a planned (live donor) transplantation.
Start immunosuppressants early in the course of rheumatoid arthritis to prevent or reduce erosions.

Drug choice
Immunosuppressants from different classes may be used individually or together in double, triple or quadruple regimens. This improves efficacy, minimises dose and adverse effects of individual drugs, or allows tailored treatment in a patient with another disease, e.g. renal impairment. Five classes of drugs are used:

- calcineurin inhibitors (cyclosporin, tacrolimus)
- corticosteroids (e.g. cortisone, dexamethasone, prednisolone)
- cytotoxic immunosuppressants (e.g. azathioprine, cyclophosphamide, methotrexate)
- immunosuppressant antibodies (e.g. antithymocyte globulins, basiliximab, infliximab)
- other immunosuppressants (everolimus, mycophenolate, sirolimus).

Organ transplantation
Transplant rejection involves T and B cell responses to foreign tissue antigens. Treatment regimens used to prevent rejection employ agents from different classes taking advantage of their complementary actions and minimising toxicity. Drug choice depends on the organ being transplanted and is tailored for each individual to minimise transplant-related morbidity.
Children and highly sensitised patients (those with pre-existing antibodies) require more intense immunosuppression than other recipients.

Double drug treatment: usually a calcineurin inhibitor with either azathioprine or mycophenolate (usually with methotrexate for bone marrow transplants).
Triple drug treatment: usually a calcineurin inhibitor, a corticosteroid and either azathioprine or mycophenolate.
Quadruple drug treatment: as for triple drug treatment plus an induction course with an immunosuppressant antibody (antithymocyte globulin, basiliximab or daclizumab).

Immunosuppression for organ transplants usually involves triple or quadruple drug treatment. The intensity of immunosuppression is initially high but tends to be reduced to a maintenance level that is determined by individual factors and the type of organ transplant. For example, in liver transplants, prednisolone is often stopped several months after transplantation and by 1 year many recipients require no more than low therapeutic doses of 1 or 2 immunosuppressants. Strategies to minimise the use of corticosteroids or calcineurin inhibitors have shown promise although the long term results are not known.
Sirolimus is being used in solid organ transplantation instead of a calcineurin inhibitor when calcineurin inhibitor toxicity precludes their use, or with a calcineurin inhibitor instead of mycophenolate or azathioprine. However,
increased mortality, graft loss and complications such as hepatic artery thrombosis within 30 days of liver transplant and fatal bronchial anastomotic dehiscence in the early post-lung transplant period, have occurred. Sirolimus is not recommended for prevention of rejection in liver or lung transplants.

Everolimus, a derivative of sirolimus, is used with cyclosporin and a corticosteroid in renal and cardiac transplantation.

Similar therapeutic effects and additive toxicity preclude using cyclosporin with tacrolimus, azathioprine with mycophenolate or sirolimus with everolimus.

**Initial treatment**

Give a corticosteroid and either azathioprine or mycophenolate (sometimes with a calcineurin inhibitor) for initial immunosuppression immediately before cadaveric donor transplantation or for several days before planned live donor transplantation.

**Acute rejection**

In acute cellular rejection high dose corticosteroids are preferred because they are effective in relatively well tolerated doses. Use an antithymocyte globulin or muromonab CD3 if corticosteroid-resistant rejection occurs or vascular rejection is proven by tissue biopsy.

Severe acute cellular rejection or vascular rejection despite immunosuppression may require an increase in baseline immunosuppression or a change in immunosuppressive agent.

**Autoimmune and inflammatory diseases**

Immunosuppressants are generally reserved for moderate-to-severe disease where end-organ damage is likely.

Rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and inflammatory myopathies are characterised by the presence of circulating antibodies, local vascular abnormalities, immune cell infiltration or antibody deposition in affected organs. Drug choice depends on the condition being treated and its severity. A second immunosuppressant is often added for corticosteroid-sparing purposes when corticosteroids are indicated.

**Prophylaxis during immunosuppression**

Prophylaxis for opportunistic infections (e.g. trimethoprim with sulfamethoxazole for P. jiroveci and Toxoplasma gondii; valaciclovir, valganciclovir or ganciclovir for CMV; oral amphotericin or nystatin for oral candidiasis) is commonly prescribed, particularly in the first 3 months after transplantation, when intense immunosuppression is required. Prophylaxis for CMV is commonly prescribed when the transplant donor is CMV-positive irrespective of the recipient’s CMV status, or when the recipient is treated with an antithymocyte globulin or muromonab CD3.

Isoniazid prophylaxis is indicated in immunosuppressed patients with latent tuberculosis infection.

H2 antagonists or PPIs may be used in transplant recipients with a history of peptic ulcer disease and when pharmacological doses of corticosteroids are used.

**Practice points**

- balance the level of immunosuppression required to preserve transplant function against the risk of post-transplant skin cancer, lymphoma, infection and end-organ toxicity
- combining myelosuppressive drugs increases the risk of anaemia; monitor haemoglobin and consider treatment if severe
- regularly examine for signs of skin cancer; patients should try to avoid direct sun exposure, use a sunscreen with a high SPF (30+) and wear a broad-brimmed hat and suitable clothing when outdoors
- ask patients to be consistent when taking medication in relation to time of day and to food
- Immunosuppression is required for the life of the transplanted organ (except some liver and bone marrow transplants and identical twin recipients)
- permanent immunosuppression may not be required in autoimmune disorders; review treatment frequently
- the patient's immune response to killed and attenuated vaccines may be inadequate while immunosuppressed; live vaccines should not be used in immunosuppressed patients; contact with faeces from a person vaccinated with oral polio vaccine within the last 6 weeks may result in systemic infection
- infections are an important cause of morbidity and mortality; they tend to be opportunistic (e.g. CMV, aspergillosis, shingles) and require early treatment; patients should know how to obtain treatment at any time
- infertility associated with chronic disease may be reversed by transplantation
- discourage pregnancy in solid organ transplant recipients for 2 years after transplantation; consider need to change drug regimen in women planning pregnancy, seek specialist advice.

**08.01.01 CALCINEURIN INHIBITORS**
**CYCLOSPORIN**

**Mode of action**
Form a complex with a cytoplasmic immunophilin which blocks the action of calcineurin in activated T cells, preventing the increase in cytokine production which normally stimulates B and T cell proliferation and differentiation.

**Indications**
Marketed:
- Prevention of kidney, liver and heart transplant rejection
- Nephrotic syndrome.
Severe active rheumatoid arthritis when renal function is unimpaired and other treatment has failed, severe psoriasis or atopic dermatitis when renal function is unimpaired and other treatment has failed.

Accepted:
- Autoimmune diseases (e.g. acute ulcerative colitis, aplastic anaemia, idiopathic thrombocytopenic purpura, Behcet's syndrome, uveitis, lupus nephritis)
- Prophylaxis of allogenic graft-versus-host disease.
To minimise antibody response in potential organ transplant recipients receiving a blood transfusion.

**Contraindications**
- Porphyria
- Allergy to solubiliser in IV preparation
- Uncontrolled infection.
- Recent exposure to shingles, chickenpox or measles without prior immunity
- Autoimmune or inflammatory diseases
- Renal impairment (except where the disease is damaging renal function and other treatment has failed)
- Uncontrolled hypertension

**Specific considerations**
- Treatment with nephrotoxic agents (e.g. NSAIDs, aminoglycosides, iodinated contrast media): additive nephrotoxicity; avoid combination if possible.
- Treatment with potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II antagonists: increases risk of hyperkalaemia; use with caution and monitor potassium concentration.
- Angiotensin II antagonists: increases risk of hyperkalaemia; use with caution and monitor potassium concentration.
- Surgery: Usual surgical antibacterial prophylaxis is appropriate. Perform dental procedures before immunosuppression or with antibacterial cover during immunosuppressive treatment.
- Children: Clearance of drug is increased; children require a higher dose per kg bodyweight than adults.
- Pregnancy: contact a specialized information centre; ADEC category C.
- Breastfeeding: Potential cyclosporin toxicity in infant; contact a specialized information centre.

**Adverse effects**
Adverse effects are commonly dose-related and reverse on dose reduction. Acceptance of adverse effects may be necessary to preserve transplant. Major dose limiting toxicity is nephrotoxicity.

Common: nephrotoxicity, hypertension, hypercholesterolaemia, tremor, paraesthesia, hyperaesthesia, neurotoxicity including seizures, elevated liver transaminases, hypomagnesaemia, hyperkalaemia, opportunistic infection, gingival hyperplasia (more common in children and adolescents), hirsutism, diarrhoea, hyperglycaemia, increased insulin requirement, diabetes, permanent renal structural changes (e.g. interstitial fibrosis).

Infrequent: headache, muscle weakness, myopathy.

Rare: confusion, seizure, coma, psychosis, haemolytic uraemic syndrome, allergy to IV formulation

Nephrotoxicity: Dose-related; consider reducing the dose or switching

Carcinogenicity: Increased risk of malignancy and lymphoproliferative disorders, particularly those associated with Epstein–Barr virus; risk increases with increased degree and duration of immunosuppression.

**Dosage**
Adjust dose according to whole blood concentrations.
Starting cyclosporin may be delayed in the immediate period after renal transplant to avoid nephrotoxicity.
Alternative immunosuppression may be required if the delay is >12–24 hours.
Give emulsified preparations twice daily. Dosing 3 times daily may be used when rapid clearance is proven (e.g. children, patients with cystic fibrosis), or when high peak concentrations cause excessive toxicity.

**Organ transplantation**
Oral, 8–15 mg/kg daily as 2 divided doses.
Oral (with diltiazem), 5–8 mg/kg daily as 2 divided doses.
Autoimmune diseases: Oral, 2.5–5 mg/kg daily as 2 divided doses.
Severe ulcerative colitis: IV, 3–5 mg/kg daily.
Prevention of allogenic graft-versus-host disease: IV, 3 mg/kg daily until oral treatment tolerated.
Dose equivalence: The IV dose is one-third to one-half of the previous total daily oral dose.

Concentration monitoring
Draw blood for cyclosporin measurement by venipuncture, not from a central line.
Aim for higher concentrations in the first 3 months after transplant and where rejection has occurred; lower concentrations where adverse effects are experienced.
There are many different assay techniques available. Avoid using nonspecific assays which measure cyclosporin plus metabolites. Concentrations obtained from nonspecific assays may not be interchangeable with the results from a specific assay.
The cyclosporin concentration 2 hours after a dose (C2) correlates better with area under the curve (AUC) than the 12-hour trough concentration (C0). There is evidence to suggest that C2 is a better indicator of adequate immunosuppression.

Trough concentrations: Whole blood specific assay, 100–300 micrograms/L.
C2 concentrations: Collect sample 2 hours (+/- 15 minutes) after a dose of cyclosporin.
Recommended C2 whole blood concentrations (for Neoral®):
- liver transplant, 600–1000 micrograms/L
- kidney transplant, 800–1500 micrograms/L.

Continuous IV infusion: Whole blood specific assay, 300–500 micrograms/L.

Administration instructions
Oral: emulsified preparation can be taken irrespective of meals.
IV: dilute IV solution to 1:20 to 1:100 in glucose 5% or sodium chloride 0.9%; infuse over 2–6 hours (more slowly if facial flushing occurs); use non–PVC-containing administration sets to avoid phthalate stripping and use short giving sets to reduce amount adsorbed.

Patient counseling
Swallow capsules whole and at the same times each day.
Clean your teeth and gums regularly.
This medicine interacts with grapefruit and many other drugs; avoid grapefruit and tell your doctor and pharmacist that you are taking this medicine before starting any new medicines.
Avoid sun exposure, wear protective clothing and use sunscreen.
If you forget to take a dose at the usual time take it as soon as you remember. If it is almost time for your next dose, skip the dose you missed. Take your next dose (normal amount) at the usual time.

Practice points
- cyclosporin dose can be reduced by using diltiazem (see Calcineurin inhibitors); tell the patient why this is being done and that the medications should not be stopped
- emulsified and non-emulsified (now rarely used) cyclosporin preparations are not interchangeable; dose adjustment may be necessary when changing formulation
- if changing the brand of emulsified cyclosporin on which a patient is stabilised, monitor cyclosporin blood concentrations (2–5 days after the swap then each week for the next 2 weeks) and look for signs of toxicity or treatment failure
- monitor renal and liver function tests, calcineurin inhibitors concentrations and BP every 2–3 months once the patient is clinically and biochemically stable
- at doses used for autoimmune disease, toxicity may be monitored by BP and renal function tests rather than cyclosporin blood concentrations
- renal biopsy may be needed to differentiate calcineurin inhibitors toxicity from the underlying disorder
- check for potential drug interactions before starting or stopping any medication
- in kidney transplantation, long term use of minimal doses of calcineurin inhibitors or carefully supervised withdrawal in selected patients also taking mycophenolate or sirolimus may improve outcomes.
Products
CYCLOSPORIN CAPS 25 MG (GENGRAF®, SANDIMMUN NEORAL®)
CYCLOSPORIN CAPS 50 MG (SANDIMMUN NEORAL®)
CYCLOSPORIN CAPS 100 MG (GENGRAF®, SANDIMMUN NEORAL®)
CYCLOSPORIN INFUSION AMPS 50 MG/ML  5 ML AMP (SANDIMMUN NEORAL®)
CYCLOSPORIN ORAL SOLUTION 100 MG/ML  50 ML BOTTLE (CYCLOMUNE®, CYCLORINE®, SANDIMMUN NEORAL®)

TACROLIMUS
Also known as FK-506.
Mode of action
Same as cyclosporin.
Indications
Marketed: Prevention of liver and kidney transplant rejection.
Accepted:
Prevention of heart and lung transplant rejection.
Rejection resistant to existing immunosuppression.
Prevention of solid organ transplant rejection.
Prevention and treatment of graft-versus-host disease in allogenic stem cell transplants.
Induction or maintenance of remission in immune and inflammatory disorders.
Contraindications
Same as cyclosporin.
Specific considerations
Risk factors for prolonged QT interval, may further prolong the QT interval and increase the risk of arrhythmia; correct underlying cause if possible; otherwise avoid combination.
Treatment with nephrotoxic agents (e.g. NSAIDs, aminoglycosides, iodinated contrast media): additive nephrotoxicity; avoid combination if possible.
Treatment with potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II antagonists: increases risk of hyperkalaemia; use with caution and monitor potassium concentration.
Hepatic impairment: Reduced metabolism and decreased drug clearance; monitor blood concentrations and patient response to tailor dosage.
Surgery: Usual surgical antibacterial prophylaxis is appropriate. Perform dental procedures before immunosuppression or with antibacterial cover during immunosuppressive treatment.
Children: Clearance of drug is increased; children require a higher dose per kg bodyweight than adults.
Pregnancy: contact a specialized information centre; ADEC category C.
Breastfeeding: Potential cyclosporin toxicity in infant; insufficient data with tacrolimus, contact a specialized information centre.
Adverse effects
Adverse effects are commonly dose-related and reverse on dose reduction. Acceptance of adverse effects may be necessary to preserve transplant. Major dose limiting toxicity is nephrotoxicity.
Common: alopecia, nephrotoxicity, hypertension, hypercholesterolaemia, tremor, paraesthesia, hyperaesthesia, neurotoxicity including seizures, elevated liver transaminases, hypomagnesaemia, hyperkalaemia, opportunistic infection, gingival hyperplasia (more common in children and adolescents), hirsutism, diarrhoea, hyperglycaemia, increased insulin requirement, diabetes, permanent renal structural changes (eg interstitial fibrosis)
Infrequent: headache, muscle weakness, myopathy
Rare: ventricular hypertrophy, cardiomyopathy, torsades de pointes, confusion, seizure, coma, psychosis, haemolytic uraemic syndrome, allergy to IV formulation
Nephrotoxicity: Dose-related; consider reducing the dose or switching to another immunosuppressant.
Carcinogenicity: Increased risk of malignancy and lymphoproliferative disorders, particularly those associated with Epstein–Barr virus; risk increases with increased degree and duration of immunosuppression.
Dosage
Adjust dose according to whole blood concentrations.
Liver transplant: Oral, 100–200 micrograms/kg daily in 2 doses.
Kidney transplant: Oral, 150–300 micrograms/kg daily in 2 doses.
Heart transplant: Oral, 50–100 micrograms/kg daily as in 2 doses.
Dose equivalence: The IV dose is one-third of the oral dose.

**Concentration monitoring**
Recommended trough (12-hour) whole blood concentrations:
- liver transplant, 5–15 micrograms/L
- kidney transplant, 8–15 micrograms/L for first 3 months, then 5–12 micrograms/L
- heart transplant, 10–15 micrograms/L initially, then 8–12 micrograms/L.

**Administration instructions**
Infuse dose over 24 hours in sodium chloride 0.9% or glucose 5% using a non–PVC-containing administration set.

**Patient counseling**
Take capsules 12 hours apart at the same time each day and in the same way (always with food or always on an empty stomach).
This medicine interacts with grapefruit and many other drugs; avoid grapefruit and tell your doctor and pharmacist that you are taking this medicine before starting any new medicines.
Avoid sun exposure, wear protective clothing and use sunscreen.
If you forget to take a dose at the usual time take it as soon as you remember. If it is almost time for your next dose, skip the dose you missed. Take your next dose (normal amount) at the usual time.

**Practice points**
- diabetes associated with tacrolimus may be reversible over time or with dose reduction
- although tacrolimus is best absorbed on an empty stomach, compliance may be improved if it is taken with a meal; emphasise the importance of taking it consistently with regard to food
- monitor renal and hepatic function and trough tacrolimus concentrations every 2–3 months once the patient is clinically and biochemically stable
- renal biopsy may be needed to differentiate tacrolimus toxicity from underlying disorder
- check for potential drug interactions before starting or stopping any medication
- in kidney transplantation, long term use of minimal doses of calcineurin inhibitors or carefully supervised withdrawal in selected patients also taking mycophenolate or sirolimus may improve outcomes

**Products**
- TACROLIMUS CAPS 1 MG (PROGRAF®)
- TACROLIMUS CAPS 5 MG (PROGRAF®)

**08.01.02 CYTOTOXIC IMMUNOSUPPRESSANTS**

**AZATHIOPRINE**

**Mode of action**
Azathioprine is metabolised to mercaptopurine which impairs cellular immunity, depresses cell proliferation and inhibits cellular inflammatory response through alterations of purine synthesis.

**Indications**
Marketed:
- Prevention of organ transplant rejection
- Immunosuppression in severe rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, autoimmune chronic active hepatitis, pemphigus vulgaris, polyarteritis nodosa, autoimmune haemolytic anaemia, refractory autoimmune thrombocytopenic purpura.

Accepted:
- Inflammatory bowel disease
- Behcet’s syndrome
- Prevention of organ transplant rejection
- Treatment or palliation of neoplastic conditions
- Autoimmune and inflammatory disorders

**Contraindications**
- Porphyria
- Hypersensitivity to azathioprine
- Immunosuppressant use in patients with a neoplastic disorder
- Uncontrolled infection.
- Recent exposure to shingles, chickenpox or measles without prior immunity

**Specific considerations**
Allopurinol inhibits mercaptopurine metabolism, increases mercaptopurine concentration and risk of bone marrow
toxicity. Reduce azathioprine dose to one-quarter to one-third of normal or consider an alternative drug (e.g., mycophenolate).

Bone marrow impairment, other myelosuppressive drugs: increased risk of severe myelosuppression and infection.

Surgery: Perform dental procedures before immunosuppression or with antibacterial cover during immunosuppressive treatment.

Renal impairment: Dose reduction may be required.

Hepatic impairment: Dose reduction may be required.

Pregnancy: Avoid use in pregnancy unless benefits outweigh risks; ADEC category D.

Breastfeeding: Opinions about safety vary; contact specialised information.

**Adverse effects**

Common: leucopenia, thrombocytopenia, anaemia, infection, alopecia, diarrhoea, anorexia, nausea and vomiting, mouth ulceration and oesophagitis.

Infrequent: hepatitis (especially with doses >2.5 mg/kg daily).

Rare: hepatic veno-occlusive disease (generally after 1–2 years and usually in males), allergic reactions (including fever, rigors, arthralgia, myalgia, rash, cough, dyspnoea, hypotension, pancreatitis, pneumonitis, interstitial nephritis, hepatic dysfunction).

Carcinogenesis: Increased incidence of skin cancers, lymphomas and mesenchymal tumours (risk may not increase when it is used in inflammatory bowel disease). Many are dose-related and reverse on dose reduction.

Fertility: Gonadal suppression, resulting in amenorrhoea or azoospermia, may not be reversible and is related to dose and duration of treatment.

**Dosage**

Monitor haematologic response (especially leucocyte count) as a guide to dosing. Bone marrow suppression limits dose.

Initially, IV/oral 2–3 mg/kg once daily; maintenance 1–3 mg/kg once daily (use minimum required to control disorder or prevent transplant rejection).

**Administration instructions**

Use appropriate cytotoxic preparation and administration precautions.

Infuse IV over 30–60 minutes as dilute solution of <2 mg/mL, or give undiluted as bolus over 1 minute with a 50 mL flush.

Highly irritant; avoid extravasation.

**Patient counseling**

Take tablets with food to help reduce stomach upset.

Swallow the tablets whole; do not break, chew or crush them.

Tell your doctor immediately if you have bleeding, increased bruising or infection.

Avoid direct sun exposure, use a sunscreen with a high SPF and wear protective clothing when outdoors.

**Practice points**

- withhold dose if white cell count is <3x10^9/L
- monitor complete blood count and liver function tests each week at first, then every 2 weeks to 3 months, depending on stability of condition; aim to maintain white cell count >3x10^9/L
- 1 in 300 metabolise azathioprine poorly; individuals are often identified when the drug is started; monitor white cell count and react promptly to a fall
- mycophenolate is used in transplantation as an alternative immunosuppressant (acts at a similar step of the immunological reaction)
- handle in accordance with cytotoxic precautions
- consider opportunistic infection when patient has signs or symptoms of infection
- avoid contact with faeces from a patient vaccinated with oral polio vaccine as systemic infection may occur
- consider collection and storage of sperm or egg before treatment when future fertility is important and doses are expected to be high and for long enough to cause infertility.

**Products**

AZATHIOPRINE SODIUM TABS 50 MG (AZATHIOPRINE®, IMURAN®)

AZATHIOPRINE SODIUM VIAL 50 MG/VIAL 1 ML VIAL (IMURAN®)

**CHLORAMBUCIL**

**Mode of action**

Interfere with cellular replication by forming cross-linkages between DNA strands.

**Indications**
Marketed: Hodgkin's and non-Hodgkin's lymphoma, Chronic lymphocytic leukaemia, Waldenström's macroglobulinaemia, Ovarian adenocarcinoma (rarely used), advanced, Breast cancer.
Accepted: Nephrotic syndrome, Systemic lupus erythematosus, lupus nephritis, immune-related ocular disease
Multiple myeloma.

Contraindications
Porphyria
Specific considerations
History of seizures: use with caution; chlorambucil may induce seizures.
Renal impairment: Reduce dose in moderate-to-severe impairment.
Hepatic impairment: Consider dose reduction in severe impairment.
Pregnancy: can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.
Breastfeeding: Insufficient data; do not use.

Adverse effects
Common: myelosuppression, nausea and vomiting.
Infrequent: abdominal discomfort, diarrhoea, stomatitis.
Rare: hallucinations, seizures, sterile cystitis, hepatotoxicity, jaundice, severe interstitial pneumonitis, Stevens–Johnson syndrome, toxic epidermal necrolysis, drug fever.
Infertility: Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Alkylating agents used in childhood may reduce fertility, particularly in males.

Myelosuppression
Secondary malignancies: All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.

Dosage
Neoplastic disorders: Consult specialist protocols. The following initial doses have been used. Further courses will depend on patient response and toxicity. Single agent, 100–200 micrograms/kg daily.
Immunosuppressant: 100–200 micrograms/kg once daily (for 8–12 weeks in nephrotic syndrome).
Moderate renal impairment: Halve dose when creatinine clearance is 20 mL/minute or less.

Counselling
Swallow whole with a glass of water; do not break, crush or chew.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

Practice points
- avoid the need to cut tablets by using different doses on alternate days
- monitor complete blood count at baseline, then each week for the first month of treatment and then every 1–3 months once stable.

Products
CHLORAMBUCIL TABS 2 MG (LEUKERAN®)

CYCLOPHOSPHAMIDE

Mode of action
Immunosuppressant properties are considered due to cytotoxic effect on lymphocytes.
Interfere with cellular replication by forming cross-linkages between DNA strands.

Indications
Marketed:
Various haematological and solid tumours
Autoimmune disorders, e.g. systemic lupus erythematosus, glomerulonephritis, rheumatoid arthritis, systemic vasculitis, Wegener's granulomatosis.
Prevention of transplant rejection
Accepted: Mobilisation of haemopoietic stem cells for subsequent infusion after myeloablative or myelosuppressive chemotherapy (high dose).

Contraindications
Porphyria, breastfeeding
Specific considerations
Treatment with daunorubicin or doxorubicin: combination with high dose cyclophosphamide can result in cardiotoxicity at lower cumulative anthracycline dose, increased risk of haemorrhagic cystitis; reduce total cumulative dose of anthracycline.
Renal impairment: Reduce dose in severe impairment.
Hepatic impairment: Biotransformation to active metabolites is reduced in severe impairment.
Pregnancy: can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.
Breastfeeding: Use is contraindicated (neutropenia has been described in breastfed infants).

Adverse effects
Common: alopecia, nausea and vomiting (moderate with low dose and severe with high dose), anorexia, haemorrhagic cystitis, myelosuppression
Infrequent: darkening of skin and fingernails, metallic taste, loss of taste
Rare: heart failure (acute onset days after high dose treatment, especially if >50 years of age or previous anthracycline exposure, may be reversible), pulmonary fibrosis (with long term high dose treatment), hepatic veno-occlusive disease and SIADH (high dose), hyponatraemia, altered mental status, seizures
Haemorrhagic cystitis: Occurs as a result of accumulation of active metabolites in the bladder. Symptoms range from mild irritation on voiding to life-threatening haemorrhagic cystitis.

Infertility
Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Primary ovarian failure has been reported with melphalan and early menopause with cyclophosphamide. Alkylating agents used in childhood may reduce fertility, particularly in males.

Secondary malignancies
All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.

Dosage
Antineoplastic: Refer to specialist protocols.
Immunosuppressant (autoimmune disorders, organ transplantation): Oral, 1–3 mg/kg once daily, reducing to minimum required to suppress disorder. Pulse IV, 0.5–1 g/m² each month for 6 months, then 0.5–1 g/m² every 3 months for 2 years.
Severe renal impairment: Reduce dose by half.

Administration instructions
Give as slow IV injection over 3–5 minutes or as a short infusion over 30–60 minutes.
Tablets should be taken in the morning and patient encouraged drinking plenty of fluids and empty bladder frequently.

Patient counseling
Swallow tablets whole with a glass of water; do not break, crush or chew.
Take tablets in the morning; drink plenty of water and empty bladder frequently. Tell your doctor if you have any signs of bladder irritation or bleeding.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occurs.

Practice points
- hydrate patient before IV infusion and throughout the day, with 2–3 L of fluid; the volume will depend on the dose of cyclophosphamide and patient tolerance of fluid load.
- high doses, e.g. 2 g/m² IV cyclophosphamide (>1 g/m² in children), or patients at high risk of cystitis, e.g. previous pelvic irradiation, require prophylactic administration of mesna
- consider microscopic urinalysis every 3–6 months and cystoscopy every 1–2 years if chronic cystitis develops or patients are at risk of latent transitional cell cancer of the bladder
- avoid the need to cut tablets by using different doses on alternate days
- cumulative bone marrow suppression may necessitate dosage reduction over time
- monitor complete blood count regularly ( frequency depends on protocol used).
Products
CYCLOPHOSPHAMIDE TABS 50 MG (ENDOXAN®)
CYCLOPHOSPHAMIDE VIAL 500 MG/VIAL (ENDOXAN®)
CYCLOPHOSPHAMIDE VIAL 1 GM/VIAL (ENDOXAN®)

METHOTREXATE

Mode of action
Folic acid antagonist. Inhibits DNA synthesis and cell replication by competitively inhibiting the conversion of folic acid to folinic acid, with cytotoxic, immunosuppressive and anti-inflammatory action.

Indications
Marketed: Treatment and palliation of solid tumours, lymphoma and leukaemia. Severe disabling psoriasis, Rheumatoid arthritis.
Accepted: Crohn's disease, Severe asthma (to enable corticosteroid reduction), Termination of ectopic pregnancy. Biliary cirrhosis, Polymyositis, dermatomyositis, Graft-versus-host disease

Contraindications
Porphyria
Severe renal impairment
Previous allergic reaction to the antimetabolite

Specific considerations
Myelosuppression: increases risk of adverse effects.
Immunodeficiency syndromes: increases immunosuppression.
GI ulceration: risk of haemorrhagic enteritis and intestinal perforation.
History of alcohol misuse: increased risk of hepatotoxicity.
Radiotherapy: increases risk of soft tissue and bone necrosis.
Treatment with colaspase: reduces effect of methotrexate if colaspase is given just before methotrexate; give colaspase 9–10 days before or just after methotrexate.
Renal impairment: Reduce dose.
Hepatic impairment: Contraindicated in psoriasis, rheumatoid arthritis, severe asthma and inflammatory bowel disease if baseline liver enzymes are >3 times the upper limit of normal.
Pregnancy: Avoid use in pregnancy unless benefits outweigh risks; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Incidence and severity of adverse effects are related to dose and frequency of administration.
Common: myelosuppression, nausea and vomiting (mild with low doses and moderate with high doses), mucositis, pulmonary toxicity, transient elevations of hepatic enzymes which may herald more severe hepatotoxicity, rash, itch, urticaria, photosensitivity.
Infrequent: malaise, fatigue, chills, fever, headache, dizziness, tinnitus, blurred vision, alopecia, ocular irritation, arachnoiditis (intrathecal administration).
Rare: serious skin reactions, leuкоencephalopathy, nephrotoxicity including renal failure, osteoporosis, skin and bone necrosis.
Myelosuppression: worsened by renal impairment, folic acid deficiency and viral illnesses. Neutropenia occurs with a nadir 7–14 days after a dose, depending on the administration schedule (more prolonged after daily administration). Thrombocytopenia and macrocytic anaemia are also common. Pancytopenia may occur and is potentially fatal.
Hepatotoxicity: Acute liver necrosis, fatty change, periportal fibrosis or cirrhosis (incidence increases with increased cumulative dose) is common with chronic, low dose therapy; reversible, acute rises in transaminase and bilirubin concentrations are common with high doses.
Pulmonary toxicity: Can develop rapidly and may be fatal. Often occurs as fever, dyspnoea, chest pain and dry, non-productive cough. Lesions such as interstitial pneumonitis and pulmonary fibrosis can occur at all doses at any time during treatment. Pulmonary toxicity may not be fully reversible; corticosteroids may relieve symptoms. Also consider the possibility of infection, eg P. jiroveci pneumonia.
Serious skin reactions: Include erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and skin ulceration/necrosis; may be fatal. Reactions can occur at all doses at any time during treatment.
Malignant lymphoma: May be caused by low dose methotrexate; stop methotrexate; if lymphoma does not regress, treat with cytotoxic chemotherapy.

Dosage
Antineoplastic: Consult specialist protocols.
Inflammatory bowel disease: IM/oral, 10–25 mg once a week.
Termination of ectopic pregnancy: IM, 50 mg/m2 repeated on day 7 if initial dose fails.
Biliary cirrhosis: Oral, 15 mg once a week.
Polymyositis, dermatomyositis: Oral, 7.5–25 mg once a week.
Renal impairment: Halve dose when creatinine clearance is 50–80 mL/minute; use extreme caution if creatinine clearance is <50 mL/minute.

Concentration monitoring
High dose methotrexate regimens, e.g. >3 g/m2, require plasma concentration monitoring. Doses for calcium folinate rescue are based on methotrexate concentration.

Administration instructions
Solution for injection is yellow.

Patient counselling
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
Take tablets strictly as directed. They should be taken once a week on the same day each week; they must not be taken every day.
Tell your doctor if you have a cough, difficulty breathing or signs of infection.
Use of some medications together with methotrexate may lead to toxicity; tell your doctor and pharmacist that you are taking this drug.
Avoid excessive or prolonged sun exposure, wear protective clothing and use sunscreen.

Practice points
- monitor complete blood count, renal and liver function tests at baseline, then each week for the first month, then once every 1–3 months
- a moderate rise in serum creatinine in the first 24 hours is common; a prolonged rise predicts reduced methotrexate elimination
- monitor patients for development of symptoms of pneumonitis, see Pulmonary toxicity; if suspected, exclude pneumonia, withdraw methotrexate and give corticosteroids
- liver biopsy may be indicated:
  - if liver enzymes are persistently raised
  - at baseline if there is a history of excessive alcohol consumption or hepatitis B or C
  - after a cumulative dose of 1.5 g and after each additional 1–1.5 g
- high dose treatment requires slow infusion, hydration and possibly alkalinisation of urine to prevent renal failure associated with crystal formation
- high dose treatment or overdose requires rescue with calcium folinate
- consider calcium folinate rescue for patients with severe mucositis and do not repeat treatment if there is residual mucositis
- nominate a particular day of the week for dosing; ensure patient does not confuse a once a week dose with a daily dose
- limited information suggests avoiding conception until 3 months after stopping treatment if either partner is treated
- sperm count may drop during treatment

Products
METHOTREXATE TABS 2.5 MG (EMTHEXATE®, METHOTREXATE®)
METHOTREXATE VIAL 1000 MG/VIAL 10 ML VIAL (METHOTREXATE®)
METHOTREXATE VIAL 5000 MG/VIAL 50 ML VIAL (METHOTREXATE®)

08.01.03 IMMUNOSUPPRESSANTS ANTIBODIES

ANTITHYMOCYTE GLOBULINS

Mode of action
Polyclonal, purified horse antibodies against human thymocyte cell surface markers, or polyclonal, purified rabbit antibodies against human T lymphoblast cell surface markers. They remove leucocytes from the circulation.
Preparations contain small amounts of antibodies with cross-reactivity against other elements of blood.

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**Indications**
Marketed: Prevention and treatment of renal transplant rejection (horse).
Accepted:
Prevention of heart, lung and liver transplant rejection (horse)
Prevention of organ transplant rejection (rabbit)
Treatment of corticosteroid-resistant rejection (horse, rabbit).
Aplastic anaemia where bone marrow transplant is contraindicated (horse).
Aplastic anaemia (rabbit), seek specialist advice.
Prophylaxis and treatment of graft-versus-host disease (horse)
Prevention of solid organ transplant rejection (horse and rabbit antithymocyte globulins, basiliximab and daclizumab).
Treatment of corticosteroid-resistant transplant rejection (muromonab CD3, horse and rabbit antithymocyte globulins)
Graft-versus-host disease (horse and rabbit antithymocyte globulins).
Aplastic anaemia where bone marrow transplant is contraindicated (horse and rabbit antithymocyte globulins).

**Contraindications**
Allergy to products derived from specific animal source (horse or rabbit).
Fluid overload (>3% above normal weight) may result in severe pulmonary oedema.
Allergy to test dose (antithymocyte globulins) or during previous exposure (all immunosuppressant antibodies)
Uncontrolled infection
Recent exposure to shingles, chickenpox or measles without prior immunity

**Specific considerations**
Treatment with myelosuppressive agents: additional myelosuppression may cause severe neutropenia, anaemia and thrombocytopenia; monitor carefully or avoid combination.
Infection: immunosuppression may increase risk and severity of infection; use caution if the person has a chronic infection or history of recurrent infections; if a severe infection occurs it may be necessary to stop treatment.
Treatment with other immunosuppressants: additive immunosuppression, increases risk of infection; also prevents or reduces the formation of antibodies against the immunosuppressant antibody.
Pregnancy: Contraindicated; no data available.
Breastfeeding: No data available

**Adverse effects**
Common: leucopenia, thrombocytopenia, thrombophlebitis, cytokine release syndrome, serious infection (particularly opportunistic), rash, arthralgia, myalgia
Infrequent: serum sickness
Rare: anaphylaxis, Cytokine release syndrome
Occurs with first and second doses usually within 1–3 hours of injection; symptoms include fever, chills, dyspnoea, chest pain, diarrhoea, nausea, vomiting, headache and hypotension; acute pulmonary oedema may occur, particularly when the patient is >3% over their lowest weight of the previous week.
Carcinogenicity: Use is associated with the development of lymphoproliferative disease..

**Dosage**
Perform skin testing for allergy before administration, see manufacturer's product information.

**Antithymocyte globulin (horse)**
Maximum
Adult, IV 30 mg/kg daily.
Child, IV 25 mg/kg daily
Prevention of acute transplant rejection: IV, 5–15 mg/kg once daily for 14 days, then on alternate days for 7 further doses.
Treatment of acute transplant rejection: IV, 10–15 mg/kg once daily for 10–14 days, then on alternate days for 7 further doses
Aplastic anaemia: IV, 10–20 mg/kg once daily for 8–14 days, then on alternate days for 7 further doses
Graft-versus-host disease: Prophylaxis, IV 15 mg/kg once daily for 10 days, starting 5 days before transplantation
Treatment (where corticosteroids have failed), IV 7–15 mg/kg once daily (or on alternate days) for 6–10 doses
Antithymocyte globulin (rabbit)
Prevention of acute transplant rejection: IV, 2–5 mg/kg once daily for 10–14 days.
Treatment of acute transplant rejection: V, 3–5 mg/kg once daily for 10–14 days.

**Administration instructions**
Infuse over 4–8 hours via a high flow vein, central line, vascular shunt or arteriovenous fistula; use a non–protein-binding in-line filter.
Patient counseling
Tell your doctor immediately if you get any signs of allergy (e.g. shortness of breath, chest tightness) or infection.

Practice points
- dialyse or diurese patient to remove excess fluid before administration
- allergic reactions may occur despite negative skin tests; in the case of rabbit antithymocyte globulin they may occur several hours after completing infusion; monitor carefully
- thrombophlebitis is likely if given via peripheral veins
- monitor complete blood count (including platelet count) daily until stable, then on alternate days until course finished
- T cell markers (CD3, CD4, CD8) may be used to monitor therapy; in some centres they are also used to determine dosing frequency
- reserve for corticosteroid-resistant or biopsy-proven vascular rejection
- consider prophylaxis against opportunistic infection (toxoplasmosis, P. jiroveci (P. carinii) and CMV, especially in CMV-negative patients receiving an organ from a CMV-positive donor)
- be aware of possibility of transmission of infectious agents (including as yet unidentified agents) since the product is prepared from animal plasma and the purification process involves contact with human blood components
- emergency equipment including adrenaline, antihistamines and corticosteroids should be easily accessible when using these agents
- , stop infusion immediately if an acute reaction occurs
- give corticosteroids (e.g. methylprednisolone), antihistamine (e.g. promethazine) and paracetamol 1 hour before the first 2 doses of antithymocyte globulins and muromonab CD3 to minimise cytokine reaction symptoms (and before the third dose if there is a marked reaction after second dose)
- during treatment with an antithymocyte globulin or muromonab CD3, at least 1 immunosuppressant is usually continued with careful monitoring; basiliximab or daclizumab are added to double or triple immunosuppressive regimes
- if calcineurin inhibitor dose is reduced or stopped during treatment with immunosuppressant antibody, it should be reinstated at therapeutic doses 2–3 days before completing antibody course, or as soon as possible after basiliximab and daclizumab dosing, to maintain immunosuppression

Products
ANTITHYMOCYTE GLOBULINS VIAL 50 MG/VIAL (NOT REGISTERED)

08.01.04 OTHER IMMUNOSUPPRESSANTS

MYCOPHENOLATE

Mode of action
Mycophenolate mofetil and mycophenolate sodium are both converted to mycophenolic acid which selectively suppresses lymphocyte proliferation and antibody formation by inhibiting inosine monophosphate dehydrogenase. Depletion of guanosine nucleotides (required for de novo purine synthesis in lymphocytes) results. Acts on the immune system at a similar level to azathioprine but by a distinct and more lymphocyte-selective mode of action

Indications
Accepted: Prevention of rejection in children >2 years with liver, heart or lung transplant (mycophenolate mofetil). Prevention of rejection in adults with liver or lung transplant (mycophenolate mofetil).

Contraindications
Allergy to solubiliser in IV preparation

Specific considerations
GI ulceration: increased risk of GI bleeding.
Phenylketonuria: mycophenolate mofetil oral suspension contains aspartame.
Renal impairment: Consider dose reduction in patients with severe chronic renal impairment.
Children: Children are at increased risk of adverse GI effects and associated weight loss.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: No data available.
Adverse effects
Adverse effects are dose-related.
Common: diarrhoea, nausea, vomiting, infections, leucopenia, anaemia, thrombophlebitis and thrombosis (IV)
Mycophenolate sodium: fatigue, headache, cough.
Infrequent: oesophagitis, gastritis, GI haemorrhage, CMV tissue invasive disease.
Carcinogenesis: It has been associated with development of post-transplant lymphoproliferative disease.

Dosage
Dose may need to be reduced in people previously treated with myelosuppressive agents.
Mycophenolate mofetil: For patients on concomitant tacrolimus, do not exceed a dose of 1 g twice daily.
Heart transplant: Adult, oral/IV, 1.5 g twice daily.
Kidney transplant: Adult, oral/IV, 1 g twice daily.
Child, oral/IV, 600 mg/m² twice daily, maximum 2 g daily.
Liver transplant: Adult, IV, 1 g twice daily initially followed by oral 1.5 g twice daily.
Other transplant: Adult, oral/IV, 1–1.5 g twice daily.
Renal impairment: Maximum 1 g twice daily in severe impairment.
Mycophenolate sodium: Tablets contain mycophenolate sodium but the dose is expressed as mycophenolic acid.
Adult, 720 mg twice daily.

Dose equivalence
720 mg of mycophenolic acid is equivalent to 1 g of mycophenolate mofetil.

Administration instructions
Mycophenolate mofetil: Reconstitute injection powder with glucose 5% and dilute further to a concentration of
6 mg/mL; infuse over at least 2 hours.
Other concentrations may be suitable but studies have only been performed using 6 mg/mL.

Patient counseling
Tell your doctor if you get diarrhoea or signs of infection.
Swallow whole and take in the same way (either always with or always without food). Take with food if you need to
prevent stomach upset.

Practice points
- monitor complete blood count (including absolute neutrophil count) each week for 1 month, then twice each
  month for 2 months, then every 1–3 months
- if neutropenia develops reduce the dose or temporarily interrupt treatment
- plasma mycophenolic acid trough concentrations may be used to guide dosage; their value is doubtful in the
  early post-transplant period (up to 6 months) unless there is a clinical indication to measure concentrations,
  e.g. GI intolerance or transplant rejection
- GI intolerance may be improved by giving mycophenolate 3 times daily
- clinical studies in renal transplant patients suggest mycophenolate is more effective than azathioprine
- cost of mycophenolate is significantly higher than azathioprine; however, increased cost may be offset by a
  reduced incidence of rejection, in particular severe rejection requiring an immunosuppressant antibody in
  the early post-transplant period.

Products
MYCOPHENOLATE TABS 360 MG (MYFORTIC®)
MYCOPHENOLATE TABS 500 MG (CELLECEPT®)

08.02 IMMUNOSTIMULANTS
08.02.01 INTERFERONS

INTERFERON ALFA
Mode of action
Binds to infected cell surface receptors inducing cellular enzymes which inhibit virus replication; suppresses cell
proliferation and enhances phagocytosis by macrophages. Augments some cytotoxic chemicals.
Indications
Marketed: Hairy cell leukaemia, Kaposi's sarcoma, Chronic myelogenous leukaemia, Follicular non-Hodgkin's
lymphoma, Cutaneous T cell lymphoma (alfa-2a only), Excessive thrombocytosis with myeloproliferative disorders
in adults (alfa-2a only), Multiple myeloma (alfa-2b only), Malignant melanoma (alfa-2b only), Chronic hepatitis B.
Chronic hepatitis C (usually with ribavirin), Advanced renal cell carcinoma (alfa-2a only).
Accepted: Acute hepatitis C, seek specialist advice.
Peginterferon alfa: Chronic hepatitis C in interferon-naive people >18 years with compensated disease (usually with ribavirin).

**Contraindications**
Decompensated hepatic disease.
Autoimmune hepatitis
Allergy to any interferon alfa or E. coli-derived proteins
Current or previous severe psychiatric condition, especially severe depression, suicidal ideation or suicide attempts.
Uncontrolled thyroid disease

**Specific considerations**
Cardiac disease: risk of arrhythmias.
Respiratory disease: may worsen.
Immunosuppressed (including transplant patients): risk of further immunosuppression.
Myelosuppressed: further myelosuppression and increased infection risk.
Bleeding disorders: thrombocytopenia may worsen condition.
Autoimmune diseases, psoriasis: risk of exacerbation.
Epilepsy: risk of exacerbation (the elderly may be more susceptible).
Renal impairment: In severe impairment may accumulate; monitor for adverse effects. Reduce dose of peginterferon alfa-2a if creatinine clearance is <40 mL/minute; avoid using peginterferon alfa-2b if it is <50 mL/minute.
Hepatic impairment: Hepatic function may worsen in severe impairment.
Children: Interferon alfa-2a injections contain benzyl alcohol; manufacturer does not recommend use in children <3 years.
Pregnancy: ADEC category B3
Breastfeeding: No data.

**Adverse effects**
Any adverse effect observed with interferon alfa is likely to occur with peginterferon alfa, although the frequency and severity may differ. Adverse effects occur more frequently in interferon-naive people.
Common: flu-like symptoms (dose-related, abate as treatment continues), anorexia, nausea, diarrhoea, abdominal pain, weight loss, alopecia, anaemia, transient leucopenia, hypotension, hypertension, palpitations, arrhythmias (common in neoplastic disorders but rare in hepatitis B and hepatitis C patients), arthralgia, myalgia, fatigue, headache.
Infrequent: dizziness, somnolence, confusion, severe depression, paraesthesia, nervousness, neuropathy, taste disturbance, diarrhoea, elevated liver enzymes, cardiomyopathy, thyroid dysfunction, thrombocytopenia.
Rare: pneumonitis, pulmonary infiltrates, hepatic dysfunction, liver failure, visual disturbances, retinopathy, seizures, coma, peripheral neuropathy, renal impairment, impaired glucose tolerance, diabetes, hypertriglyceridaemia, aplastic anaemia, rhabdomyolysis, autoimmune disease, e.g. vasculitis, rash, hypersensitivity including anaphylaxis.

**Dosage**
Doses and duration of treatment vary according to the condition being treated. Usually given SC (interferon alfa-2b may be given IV).

**Patient counseling**
Tell your doctor immediately if you get any jaundice (yellowing of skin and whites of eyes) or easy bruising, or are feeling more depressed or sad than usual or notice any difficulty in breathing or with your vision. This medication may make you feel tired, sleepy or confused: avoid driving or using machinery if you feel like this. Warm by holding in your hand for a few minutes or leave at room temperature for 30 minutes before injecting.

**Practice points**
- nomenclature 2a and 2b refers to slight differences in the amino acid sequences; these are not thought to be clinically significant
- minimise flu-like reaction by dosing at bedtime and premedicating with paracetamol
- monitor complete blood count, electrolytes, renal function and liver function at baseline, at 2 and 4 weeks, then each month; patients with renal or hepatic impairment may benefit from more intense monitoring, particularly in the first 3 months of treatment
- perform thyroid function tests at baseline and every 3 months
- obtain baseline eye examination in all patients; monitor vision periodically in those predisposed to retinopathy, e.g. diabetics
- monitor ECG in patients with past or present cardiac abnormalities
- reduce dose (or stop treatment) if necessary because of adverse effects, eg depression, neutropenia, hepatic decompensation
- ensure adequate hydration (hypotension can occur)
- check for pulmonary infiltrates if respiratory symptoms develop (x-ray required); monitor the person closely
- check for depression regularly (consider using a standard questionnaire, especially if there are symptoms); consider referral for treatment

**Products**

INTERFERON ALFA-2B PEN 18 M IU/PEN (INTRON-A®)
INTERFERON ALFA-2B PEN 30 M IU/PEN (INTRON-A®)

**08.02 02. OTHER IMMUNOSTIMULANTS**

**ALDESLEUKIN**

**Mode of action**
Recombinant variant of interleukin-2 binds both chains of the interleukin-2 receptor located on the surface of T and B lymphocytes, stimulating cell proliferation. Production of interferon gamma and activity of natural killer cells is also enhanced.

**Indications**
Accepted: Metastatic renal cell carcinoma; Melanoma; Thymoma, Bone marrow transplantation; HIV.

**Contraindications**
Compromised cardiac function.
Compromised lung function.
Uncontrolled infection.
Cerebral metastasis.

**Specific considerations**
Seizure history: risk of seizure recurrence or exacerbation.
Autoimmune and inflammatory disorders: risk of recurrence, exacerbation or precipitation.
Eastern Cooperative Oncology Group (ECOG) performance status >: toxicity outweighs benefits.
Treatment with nephrotoxic, myelotoxic, cardiotoxic or hepatotoxic agents: additive effects; avoid combination.
Renal impairment: Nephrotoxicity more severe and prolonged with pre-existing impairment.
Elderly: Reduced tolerance to adverse effects due to reduced physiological reserve.
Pregnancy: seek specialist advise; ADEC category C.
Breastfeeding: No data.

**Adverse effects**
Adverse effects are related to dose and route of administration. Lower doses and SC use are associated with fewer adverse effects than high doses and IV route. Most are self limiting and usually reverse or improve 2–3 days after stopping treatment.
Common: pulmonary oedema appearing as dyspnoea; neurological effects including headache, confusion, disorientation, drowsiness, speech difficulties, ataxia, hallucinations, cortical blindness, seizures, coma; fever, flu-like symptoms such as malaise, rigors, myalgia; infection; thrombocytopenia and anaemia; thyroid dysfunction (hypothyroidism preceding hyperthyroidism) and hyperglycaemia; pain, swelling, cellulitis, nodules and induration, necrosis with SC injection; capillary leak syndrome with high dose IV.
Capillary leak syndrome: More common with high doses given IV; causes fluid retention and hypotension with symptoms including weight gain, reduced organ perfusion with resultant organ dysfunction and possibly infarction, oliguria, uraemia, anuria; recovery occurs over hours to days.
Antibody formation: Antibody formation against aldesleukin with unknown clinical significance.

**Dosage**
Consult specialist protocols. Doses are withheld rather than reduced when adverse effects occur.

**Patient counseling**
Life-threatening adverse effects may occur. Some adverse effects are expected and indicate the drug is working. Tell your doctor if you have difficulty breathing or pain in the chest.

**Practice points**
- SC administration has replaced IV infusion (equal efficacy and reduced adverse effects)
- change injection site and apply cold or warm compresses to minimise local reaction
- as effective as interferon alfa in renal cell carcinoma but with worse adverse effects
• before treatment assess pulmonary and cardiac function and obtain cerebral scan to exclude patients with contraindications; monitor thyroid function at baseline and every 3 months; monitor renal and liver function and blood glucose at baseline and daily during treatment
• onset of adverse effects may be immediate; paracetamol and corticosteroids may be used to manage symptoms of adverse effects (however, corticosteroids may antagonise antineoplastic effects); use fluid replacement cautiously.

**Products**

**ALDESLEUKIN VIAL 18 MU/VIAL (NOT REGISTERED)**

**08.03. CYTOTOXIX DRUGS**

**08.03.01 ALKYLATING DRUGS**

**BUSULFAN**

**Mode of action**

Interfere with cellular replication by forming cross-linkages between DNA strands.

**Indications**

Marketed: Chronic myeloid leukaemia; Myelofibrosis; Polycythaemia vera and essential thrombocythaemia.
Accepted: Mobilisation of haemopoietic stem cells for subsequent infusion after myeloablative or myelosuppressive chemotherapy (high dose).

**Contraindications**

Porphyria.

**Specific considerations**

Treatment with thioguanine: has resulted in hepatotoxicity; avoid combination.

Pregnancy: can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.

Breastfeeding: Insufficient data; do not use.

**Adverse effects**

Common: Low dose, mylosuppression, nausea and vomiting, diarrhoea, anorexia and weight loss, hyperpigmentation of the skin.

High dose, hepatic veno-occlusive disease (usually in combination with other cytotoxics or radiotherapy), tumour lysis syndrome, alopecia, amenorrhoea, stomatitis, diarrhoea or constipation, dry mouth, oesophagitis, dyspepsia, dizziness, blurred vision, intermittent muscle twitching, seizures, insomnia, confusion, delirium, hyperglycaemia, hypokalaemia, hypocalcaemia, alopecia, skin reactions with concurrent radiotherapy.

Rare: Low dose, Addison-like syndrome, pulmonary fibrosis, erythema nodosum, erythema multiforme, cataracts, gynaecomastia.

High dose, raised hepatic enzymes (bilirubin, ALP, transaminases), pulmonary fibrosis, cardiovascular effects, dyspnoea and cough, interstitial pneumonitis, increase in serum creatinine.

Addison-like syndrome: Addison-like syndrome (anorexia, vomiting, diarrhoea, weight loss, weakness, fatigue, hypotension, hyperpigmentation) may occur following long term treatment. Adrenal function usually remains normal. It may resolve after stopping busulfan.

Pulmonary fibrosis: Diffuse or progressive pulmonary fibrosis is rare, usually insidious in onset, but may be acute. Presents as progressive difficulty in breathing and a persistent nonproductive cough and fever. May be reversible if detected before clinical symptoms manifest and the drug is stopped, but may progress to respiratory failure.

Infertility: Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Primary ovarian failure has been reported with melphalan and early menopause with cyclophosphamide. Alkylating agents used in childhood may reduce fertility, particularly in males.

Secondary malignancies: All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers

**Dosage**

Consult specialist protocols. The following initial doses have been used. Further courses will depend on patient response and toxicity.

Chronic myeloid leukaemia: Induction of remission, 60 micrograms/kg (maximum 4 mg) daily.

Maintenance, usually 0.5–2 mg daily.

Polycythaemia vera and essential thrombocythaemia: Induction of remission, 4–6 mg daily. Maintenance, approximately half induction dose.
Myelofibrosis: Initially, 2–4 mg daily.
Mobilisation of haemopoietic stem cells for subsequent infusion after myeloablative or myelosuppressive chemotherapy: Oral, 3.5–4 mg/kg daily for 4 days. IV, 0.8 mg/kg ideal or actual bodyweight (whichever is less) every 6 hours for 16 doses (4 days).

**Patient counselling**
Swallow tablets whole with a glass of water; do not break, crush or chew. Tell your doctor if you have difficulty in breathing or a persistent cough or bruising.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

**Practice points**
- stop busulfan if there are signs of pulmonary toxicity, platelet count falls sharply or purpura develops
- monitor complete blood count regularly during chronic therapy; busulfan may cause irreversible bone marrow depression that may not be apparent for several months after stopping treatment
- prophylactic use of anticonvulsants during high dose therapy is common; phenytoin is effective and clonazepam has been used in children.

**Chronic myeloid leukaemia**
- Ineffective in the blastic phase
- Induction, stop treatment when white cell count falls to 15–25x10⁹ cells/L (monitor each week); stop busulfan earlier if platelets fall below 100x10⁹ cells/L
- measure complete blood count at least every 4 weeks; aim for white cell count of 10–15x10⁹ cells/L
- maintenance, consider giving continuous maintenance treatment if white cell count returns to 50x10⁹ cells/L.

**Products**
BUSULFAN TABS 2 MG (MYLERAN®)

**IFOSFAMIDE**

**Mode of action**
Interfere with cellular replication by forming cross-linkages between DNA strands.

**Indications**
Active against a range of tumours including sarcomas, lymphomas, testicular, ovarian, cervical, breast and lung cancer

**Specific considerations**
Cystitis: increases risk of haemorrhagic cystitis.
Patients with 1 kidney: increased risk of adverse effects with high dose ifosfamide.
Heart failure: increases risk of neurotoxicity if unable to tolerate fluid load for hydration.
Treatment with cisplatin: increases risk of myelosuppression and neurotoxicity; monitor closely for adverse effects.
Renal impairment: Reduce dose in severe impairment. Renal function may worsen due to proximal and distal tubule damage; monitor closely.
Hepatic impairment: Biotransformation to active drug may be reduced in severe impairment; may increase CNS toxicity of ifosfamide.
Surgery: Do not give until 3 months after nephrectomy.
Children: Incidence of nephrotoxicity increases with cumulative doses of 60–100 g/m².
Pregnancy: can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.
Breastfeeding: Insufficient data; do not use.

**Adverse effects**
Common: myelosuppression, moderate nausea and vomiting, anorexia, diarrhoea, constipation, alopecia, somnolence, confusion, haemorrhagic cystitis.
Infrequent: reduced creatinine clearance, proteinuria, renal tubular acidosis and phosphaturia.
Rare: hallucinations, seizures, acute cardiotoxicity (high doses), haematemesis, weakness, thrombophlebitis, exacerbation of radiodermatitis, renal impairment leading to Fanconi syndrome (cumulative, total dose >72 g/m²), cerebellar and motor dysfunction, peripheral sensory neuropathies, coma.
Haemorrhagic cystitis: Occurs as a result of accumulation of active metabolites in the bladder. Symptoms range from mild irritation on voiding to life-threatening haemorrhagic cystitis. Greater risk with current or prior radiotherapy or concurrent bladder infection.
Infertility: Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Primary ovarian failure has been reported with melphalan and early menopause with cyclophosphamide. Alkylating agents used in childhood may reduce fertility, particularly in males. Secondary malignancies: All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.

**Dosage**

See specialist protocols

The following initial dose has been used in combination therapy. Further courses will depend on patient response and toxicity.

**IV infusion:** 1.6–2 g/m² daily for 5 days.

**Administration instructions**

Short IV infusion over 30–60 minutes or continuous infusion over 24 hours.

**Patient counseling**

This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

Drink plenty of water and empty bladder frequently during treatment. Tell your doctor if you have any signs of bladder irritation or bleeding.

**Practice points**

- give with mesna and adequate hydration (2 L fluid daily) to induce diuresis
- obtain urinalysis before each dose and withhold dose if >10 red cells/high power field or there is evidence of UTI
- high doses (5–8 g/m2) may cause fluid retention; monitor fluid balance and give frusemide if necessary
- obtain complete blood count, serum creatinine and albumin before each dose; serum albumin <30 g/L with elevated serum creatinine is associated with ifosfamide neurotoxicity

**Products**

- IFOSFAMIDE VIAL 1 GM/VIAL (HOLOXAN®)
- IFOSFAMIDE VIAL 2 GM/VIAL (HOLOXAN®)

**LOMUSTINE**

Also known as CCNU

**Mode of action**

Interfere with cellular replication by forming cross-linkages between DNA strands.

**Indications**

- Brain tumours, primary and metastatic
- Hodgkin's disease, second line

**Specific considerations**

- Pregnancy: can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.
- Breastfeeding: Insufficient data; do not use.

**Adverse effects**

Common: myelosuppression, moderate nausea and vomiting, anorexia.

Infrequent: stomatitis, alopecia, transient elevation of liver function tests, elevation of serum creatinine.

Rare: pulmonary infiltration and/or fibrosis occurring after >6 months of therapy and cumulative doses of 600–1000 mg.

Infertility: Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Primary ovarian failure has been reported with melphalan and early menopause with cyclophosphamide. Alkylating agents used in childhood may reduce fertility, particularly in males.

Secondary malignancies: All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.

**Dosage**
Consult specialist protocols. The following initial doses have been used in combination therapy. Further doses will depend on patient response and toxicity. 100–130 mg/m² as a single dose or in divided doses over 3 days.

**Patient counselling**
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one. This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Swallow whole; do not open or chew the capsules.
Taking this medicine on an empty stomach may help to reduce the severity of nausea and vomiting that it often causes. Take it at least half an hour before, or 2 hours after, food.
Tell your doctor if you have difficulty in breathing or a persistent cough.

**Practice points**
- Lomustine absorption is rapid; readministration not required if vomiting occurs >45 minutes after administration.
- Obtain complete blood count, serum creatinine and liver function before each cycle.

**Products**
LOMUSTINE TABS 20 MG (NOT REGISTERED)

**Melphalan**
Also known as phenylalanine mustard

**Mode of action**
Interfere with cellular replication by forming cross-linkages between DNA strands.

**Indications**
Marketed: Multiple myeloma, Ovarian cancer, advanced (rarely used), Breast cancer, metastatic, refractory (rarely used), Polycythaemia vera, Malignant melanoma of the extremities (by isolated limb perfusion), Soft tissue sarcoma (by isolated limb perfusion).
Accepted: Mobilisation of haemopoietic stem cells for subsequent infusion after myeloablative or myelosuppressive chemotherapy (high dose).

**Contraindications**
Allergy to melphalan or busulfan.

**Specific considerations**
Renal impairment: Reduce dose in moderate-to-severe impairment; do not use high dose therapy.
Pregnancy: can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.
Breastfeeding: Insufficient data; do not use.

**Adverse effects**
Common: myelosuppression, nausea and vomiting, diarrhoea, alopecia, allergic skin reactions.
Infrequent: stomatitis, pulmonary fibrosis and interstitial pneumonitis, skin ulceration at IV injection site and skin necrosis (rarely requiring skin grafting).
Rare: anaphylaxis, hepatic veno-occlusive disease (IV), SIADH.
Infertility: Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Primary ovarian failure has been reported with melphalan and early menopause with cyclophosphamide.
Alkylating agents used in childhood may reduce fertility, particularly in males.
Secondary malignancies: All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.

**Dosage**
Consult specialist protocols. The following initial doses have been used. Further courses will depend on patient response and toxicity.
Multiple myeloma: Oral, 150 micrograms/kg in divided doses daily for 4–7 days with prednisolone.
High dose therapy: IV, 100–200 mg/m² with autologous haemopoietic stem cell support.
Moderate-to-severe renal impairment: Halve IV dose and consider reducing oral dose.

**Administration instructions**
Give injection or short infusion into side arm of fast running infusion of sodium chloride 0.9%.
Patient counselling
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Swallow tablets whole with a glass of water; do not break, crush or chew.
Take tablets on an empty stomach, at least half an hour before, or 2 hours after, food.
Tell your doctor if you have difficulty in breathing or a persistent cough.

Practice points
- the IV formulation is only marketed for multiple myeloma
- allergic reactions are more common after several courses of IV therapy
- absorption after oral therapy is variable and may be poor; if no myelotoxicity occurs, absorption is likely to be unsatisfactory.

Products
MELPHALAN TABS 2 MG (ALKERAN®)
MELPHALAN VIAL 50 MG/VIAL (NOT REGISTERED)

TEMOZOLOMIDE
Mode of action
Interferes with cellular replication by forming cross-linkages between DNA strands.

Indications
Marketed: Recurrence of anaplastic astrocytoma (including glioblastoma multiforme) after standard therapy
Newly diagnosed glioblastoma multiforme, with radiotherapy, then as adjuvant treatment. Metastatic malignant melanoma
Accepted: High grade gliomas, first line with radiotherapy or recurrence after radiotherapy

Contraindications
Allergic reaction to dacarbazine or temozolomide

Specific considerations
Elderly: Risk of neutropenia and thrombocytopenia is increased.
Children: There is limited experience in children with glioma, seek specialist advice.
Pregnancy: can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.
Lactation: Insufficient data; do not use.

Adverse effects
Common: myelosuppression, lymphopenia, moderate nausea and vomiting, headache, fatigue, dyspnoea, fever, pain, malaise, weight loss, rigors.
First dose use in gliomas, neurological disturbance including weakness, dysphasia, headache, confusion, seizure and obtundation
Infertility: Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Primary ovarian failure has been reported with melphalan and early menopause with cyclophosphamide.
Alkylating agents used in childhood may reduce fertility, particularly in males.
Secondary malignancies: All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.

Dosage
Consult specialist protocols. The following initial doses have been used. Further courses depend on patient response and toxicity.
Recurrent astrocytoma: Previous chemotherapy, 150 mg/m2 once daily for 5 days/28-days for first cycle, then 200 mg/m2 once daily for 5 days/28-day cycle. Chemotherapy naive, 200 mg/m2 once daily for 5 days/28-day cycle.
Newly diagnosed glioblastoma multiforme: 75 mg/m2 daily for 42 days with radiotherapy, then after 4 weeks, 100–200 mg/m2 once daily for 5 days/28-day cycle for 6 cycles.
Metastatic malignant melanoma: 200 mg/m2 once daily for 5 days/28-day cycle.

Patient counselling
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding
occur. Swallow whole with a glass of water; do not open or chew the capsules. Take on an empty stomach, at least an hour before food.

**Practice points**
- temozolomide is a pro-drug with active metabolites similar to those produced by dacarbazine
- monitor complete blood count before each cycle or weekly during use with radiotherapy for newly diagnosed glioblastoma multiforme
- prophylaxis against *Pneumocystis jiroveci pneumonia (PCP)* is required during combined treatment with temozolomide and radiotherapy

**Products**
- TEMOZOLAMIDE CAPS 20 MG (TEMODAL®)
- TEMOZOLAMIDE CAPS 100 MG (TEMODAL®)
- TEMOZOLAMIDE CAPS 250 MG (TEMODAL®)

**08.03.02 ANTHRACYCLINES**

**BLEOMYCIN**

**Mode of action**
Inhibits DNA and to a lesser extent RNA synthesis, produces single and double strand breaks in DNA possibly by free radical formation.

**Indications**
Marketed: Palliative or adjunctive treatment in embryonal cell carcinoma of the testis and choriocarcinoma, Hodgkin's and other lymphomas, squamous cell carcinoma of the skin, head and neck, oesophagus, penis, larynx, cervix, bronchus, mycosis fungoides. Sclerosing agent in malignant pleural effusion.
Accepted: Kaposi's sarcoma.

**Contraindications**
Acute lung infection or severely compromised lung function.
Previous allergic reaction to bleomycin.

**Specific considerations**
Treatment with cisplatin: reduces clearance of bleomycin; increases pulmonary toxicity; monitor closely.
Renal impairment: Reduce dose in mild-to-moderate impairment; do not use in severe impairment.
Surgery: Lung is sensitised to oxygen and pulmonary fibrosis may develop; use reduced oxygen concentrations during subsequent anaesthesia.
Elderly: Increased risk of pulmonary toxicity; reduce maximal cumulative exposure.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: Contraindicated; passes into breast milk.

**Adverse effects**
Common: rash, erythema, itch, vesiculation, hyperkeratosis, hyperpigmentation (particularly of skin folds), mouth ulcers, alopecia; hypersensitivity reaction (more common in lymphoma patients), e.g. fever and occasionally rash and angioedema (may be delayed several hours); pneumonitis progressing to pulmonary fibrosis (dose limiting effect, nausea and vomiting.
Infrequent: Raynaud's phenomenon.
Rare: acute chest pain during infusion (may not occur with subsequent doses).
Pulmonary toxicity: Pulmonary toxicity occurs in approximately 10% of patients, may progress to pulmonary fibrosis and may result in death; increased risk if >70 years, cumulative dose> 400 000 international units, mediastinal radiotherapy, pre-existing lung disease, history of smoking. Earliest symptoms and signs include dyspnoea and cough and fine rales.

**Dosage**
Consult specialist protocols
Lymphoma patients must receive a test dose of 1000–5000 international units before the first 2 doses; if no evidence of allergy after 4–6 hours, the remainder of the per protocol dose may be given.
Maximum cumulative dose, 300 000–400 000 international units
Intrapleural, 30 000–60 000 international units single dose in 100 mL sodium chloride 0.9%.
Renal impairment: Reduce dose by one quarter in mild-to-moderate impairment.

**Dose equivalence**
1000 international units bleomycin is equivalent to 1 USP unit. Each mg contains 1.5–2 USP units (some older protocols state dose in mg).
Administration instructions
May be given IM, SC, intra-arterially, IV or intrapleurally.
Give IV over 10 minutes. IM may be given mixed with 1% lignocaine. Test dose must be given before first and second doses in all lymphoma patients.

Practice points
- increased efficacy if given before radiation
- perform chest x-ray at baseline, then each week during therapy and for 4 weeks after
- pulmonary diffusion capacity for carbon monoxide used as an indicator of subclinical pulmonary toxicity; stop if it falls to <30–35% of pretreatment value
- prompt treatment of pneumonitis with corticosteroids may prevent progression to fibrosis
- bleomycin sensitises lung tissue to high concentration oxygen; use room air concentrations during surgery
- monitor plasma creatinine at baseline and before each cycle.

Products
BLEOMYCIN AMPS 15 MG/AMP (AS HCL) (BLEOCIN®)

DACTINOMYCIN

Mode of action
Complexes with DNA interfering with DNA-dependent RNA synthesis; also has immunosuppressant properties.

Indications
Wilms' tumour
Rhabdomyosarcoma
Ewing's sarcoma, sarcoma botyroides and primitive neuroectodermal tumours (PNET)
Carcinoma of the testis and uterus

Specific considerations
Previous or current radiotherapy: effects of radiation may be worsened.
Children: Increased incidence of adverse effects; use only where benefits outweigh risk in children <6–12 months old.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: Contraindicated.

Adverse effects
Common: myelosuppression, nausea and vomiting (onset within a few hours and lasting up to 24 hours), mucositis, diarrhoea, fever, malaise, myalgia, alopecia, rash (acne and skin eruptions, particularly in adolescents).
Rare: anaphylaxis.

Myelosuppression: Affects mainly white cells and platelets; nadir of white cell and platelet count occurs 14–21 days after a dose with recovery in 21–25 days.

Other: Extravasation may result in severe damage; debridement and skin grafting may be required.
Radiation effects may be potentiated by dactinomycin. Erythema of the radiation site may be followed by hyperpigmentation, oedema, desquamation, vesiculation and, rarely, necrosis. Severe mucositis may result if radiation includes mucous membranes.

Dosage
Consult specialist protocols. The following initial doses have been used with other drugs:
Adult, IV, 500 micrograms daily for 5 days.
Child, IV, 15 micrograms/kg daily for 5 days.
Further doses depend on patient response and toxicity.

Administration instructions
Solution for injection is yellow.
Do not use in-line filters as dactinomycin is removed by those made from cellulose esters.
Give as slow IV bolus at concentration of 25 micrograms/mL into the side arm of a fast, freely running infusion of sodium chloride 0.9% or glucose 5%. Avoid extravasation.

Patient counselling
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
It may also cause you to bruise and bleed more easily; tell your doctor if this occurs.

Practice points
- monitor complete blood count before each course of treatment
DOXORUBICIN
Also known as hydroxydaunorubicin.

Mode of action
Cell cycle nonspecific action inhibiting DNA and DNA-dependent RNA synthesis by intercalation between base pairs with uncoiling of the helix. Interferes with topoisomerase II function, preventing re-ligation of DNA strand breaks. Peroxide and free radical production may also contribute to cytotoxicity. Anthracyclines also have immunosuppressive activity and mitozantrone can induce apoptosis in leukaemic cells.

Indications
Conventional: Widely used in haematologic and solid tumours.
Pegylated liposomal
Metastatic breast cancer
AIDS-related Kaposi's sarcoma, advanced or refractory
Ovarian cancer, advanced, after failure of platinum-based chemotherapy.

Contraindications
Maximal anthracycline exposure
Cardiac toxicity from any anthracycline exposure
Intrathecal, IM or SC injection

Specific considerations
Treatment with high dose cyclophosphamide: cardiotoxicity at lower cumulative doxorubicin dose, increased risk of haemorrhagic cystitis; reduce total cumulative dose of doxorubicin.
Current radiotherapy: enhances skin and mucous membrane toxicity.
Recent radiotherapy in previous few weeks: radiation recall may occur.
Previous radiotherapy to chest region: see Cardiac toxicity.
Cardiac disease, reduced cardiac reserve: cardiac toxicity may be enhanced.
Previous anthracycline exposure: cumulative cardiac toxicity; when calculating cumulative dose include any previous anthracycline exposure if changing to another anthracyline.
Treatment with trastuzumab: increases cardiotoxicity disproportionately to risk with individual anthracycline; avoid anthracycline for 22 weeks after trastuzumab and monitor cardiac function
Elderly: Cardiotoxicity may occur at lower cumulative dose.
Children: Cardiotoxicity may lead to heart failure in early adulthood.
Hepatic impairment: Dose reduction required in moderate-to-severe impairment.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Common: Conventional and pegylated liposomal, stomatitis, oesophagitis, nausea and vomiting starting after 3–6 hours and lasting from several to 24 hours, alopecia starting 1–2 weeks after dosing, rash, itch
Pegylated liposomal, rapid administration may cause back pain, flushing and chest tightness generally in the first 5 minutes; symptoms resolve upon stopping infusion and do not recur when infusion is restarted at a slower rate; palmar-plantar erythrodysoaesthesia (swelling, pain, erythema, possibly desquamation)
Intravesical administration, tends not to cause systemic toxicity but may cause chemical cystitis, contraction of bladder, haematuria, pain, frequency and urgency of micturition.
Infrequent: Conventional and pegylated liposomal, conjunctivitis, lacrimation and facial flushing, hyperpigmentation of nails, buccal mucosa and skin folds, fever, chills
Myelosuppression: Myelosuppression is common, affecting white cells, and to a lesser degree, platelets and red cells.
The white count nadir occurs about 10 days after a dose, with recovery by about 21 days.
Cardiac toxicity: May be acute or chronic: acute transient conduction abnormalities and arrhythmias are common; chronic cumulative dose-related damage to myofibrils reducing cardiac function starts about 1–6 months after initiation, may be irreversible and fatal.
Mediastinal radiation, age <4 or >60 years, current administration of cardiotoxic agents and pre-existing cardiac disease increase the risk of cardiac toxicity.
Extravasation: Severe local tissue necrosis, severe cellulitis, thrombophlebitis or painful induration may result from extravasation. Liposomal formulations cause less local inflammation. Mitozantrone rarely causes necrosis. If extravasation is suspected, stop injection immediately, attempt to aspirate residual drug, institute extravasation
treatment, resite IV access to another limb.
Secondary malignancies: Anthracycline use may be associated with later development of drug-resistant secondary malignancies.

**Dosage**
Consult specialist protocols
Conventional: Intravesical, 50–100 mg in 50–100 mL sodium chloride 0.9% each month.
Pegylated liposomal
Kaposi’s sarcoma, IV 20 mg/m2.
Breast and ovarian cancer, IV 50 mg/m2
Further courses depend on patient response and toxicity.

**Total cumulative dose**
Adult, 550 mg/m2 (400–450 mg/m2 if elderly, concurrent high dose cyclophosphamide, chest irradiation or hypertensive cardiomegaly).
Child, 300–350 mg/m2.
Pegylated liposomal doxorubicin, higher cumulative doses may be tolerated.

**Administration instructions**
Conventional
Solution is red
IV, by injection or short infusion into side arm of a fast running sodium chloride 0.9% infusion. May also be given intra-arterially.
Intravesical, retain for 1 hour, changing position every 15 minutes (from side-to-side, lying and standing) to ensure complete bladder exposure.
Pegylated liposomal: dilute before use in glucose 5%. Infusion is translucent red.
Kaposi’s sarcoma, IV infusion over 30 minutes.
Breast and ovarian cancer, infuse initial dose at a rate <1 mg/minute; if no infusion reaction, infuse subsequent doses over 60 minutes. Infuse doses <90 mg in 250 mL, >90 mg in 500 mL.

Anthracyclines are vesicant; avoid extravasation

**Patient counselling**
Urine may appear red for 1–2 days after dose.
Tell your doctor or nurse immediately if you feel any pain, stinging or burning during the injection or infusion.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

**Practice points**
Pegylated liposomal
- this formulation produces increased concentrations of the drug in the lesions of Kaposi’s sarcoma compared with the conventional form
- may be less cardiotoxic than conventional doxorubicin and may cause less tissue necrosis but the usual precautions to avoid extravasation should be used
- monitor complete blood count, liver function and renal function at baseline and before each cycle
- monitor ECG and left ventricular ejection fraction at baseline and after every 3 cycles
- persistent QRS voltage reduction may indicate cardiotoxicity
- add up all doses of anthracycline(s) to estimate cardiotoxic dosage limit
- scalp cooling to reduce hair follicle toxicity and subsequent loss during drug administration is controversial and may reduce drug transport, allowing the development of metastatic disease in the area

**Products**
DOXORUBICIN-LIPOSOMAL VIAL 20 MG/VIAL (CAELYX®)
DOXORUBUCIN VIAL 10 MG/VIAL (AS HCL) (ADRIBLASTINA®, ADRIM®, DOXORUBICIN EBEWE®, DOXORUBIN®, A.D.MYCIN®)

DOXORUBUCIN VIAL 50 MG/VIAL (AS HCL) (ADRIBLASTINA®, ADRIM®, DOXORUBICIN EBEWE®, DOXORUBIN®, A.D.MYCIN®, D-RUBICIN®, DOXORUBICIN TEDEC®)
IDARUBICIN

Mode of action
Cell cycle nonspecific action inhibiting DNA and DNA-dependent RNA synthesis by intercalation between base pairs with uncoiling of the helix. Interfere with topoisomerase II function, preventing re-ligation of DNA strand breaks. Peroxide and free radical production may also contribute to cytotoxicity. Anthracyclines also have immunosuppressive activity and mitozantrone can induce apoptosis in leukaemic cells.

Indications
Marketed: Acute myeloid leukaemia.
Accepted: Acute lymphoblastic leukaemia (ALL), Breast cancer, Multiple myeloma, Non-Hodgkin's lymphoma.

Contraindications
Maximal anthracycline exposure.
Cardiac toxicity from any anthracycline exposure.
Intrathecal, IM or SC injection

Specific considerations
Current radiotherapy: enhances skin and mucous membrane toxicity.
Recent radiotherapy in previous few weeks: radiation recall may occur.
Previous radiotherapy to chest region: see Cardiac toxicity.
Cardiac disease, reduced cardiac reserve: cardiac toxicity may be enhanced.
Previous anthracycline exposure: cumulative cardiac toxicity; when calculating cumulative dose include any previous anthracycline exposure if changing to another anthracycline.
Treatment with trastuzumab: increases cardiotoxicity disproportionately to risk with individual anthracycline; avoid anthracycline for 22 weeks after trastuzumab and monitor cardiac function.
Renal impairment: Dose reduction required in severe impairment.
Elderly: Risk of enhanced myelosuppression, mucositis and cardiac toxicity.
Hepatic impairment: Dose reduction required in moderate-to-severe impairment.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Common: myelosuppression, lassitude, stomatitis, oesophagitis, nausea and vomiting starting after 1–14 hours and lasting 6 hours, possibly several days; diarrhoea, particularly with oral therapy; alopecia starting 2 weeks after dosing; red–orange urine for 1–2 days after dosing; raised liver transaminases and bilirubin, particularly if used with cytarabine.
Rare: enterocolitis with perforation.
Myelosuppression: Myelosuppression is common, affecting white cells, and to a lesser degree, platelets and red cells.
The white count nadir occurs about 10 days after a dose, with recovery by about 21 days.
Cardiac toxicity: may be acute or chronic cardiotoxicity; acute transient conduction abnormalities and arrhythmias are common; chronic cumulative dose-related damage to myofibrils reducing cardiac function start about 1–6 months after initiation, may be irreversible and fatal.
Mediastinal radiation, age <4 or >60 years, current administration of cardiotoxic agents and pre-existing cardiac disease increase the risk of cardiac toxicity.
Extravasation: Severe local tissue necrosis, severe cellulitis, thrombophlebitis or painful induration may result from extravasation. Liposomal formulations cause less local inflammation. Mitozantrone rarely causes necrosis. If extravasation is suspected, stop injection immediately, attempt to aspirate residual drug, institute extravasation treatment, resite IV access to another limb.
Secondary malignancies: Anthracycline use may be associated with later development of drug-resistant secondary malignancies.

Dosage
Consult specialist protocols
Severe mucositis: If severe mucositis occurs reduce dose by one quarter.
Severe renal impairment: Refer to specialist protocols.
Severe hepatic impairment: Reduce dose by half.
Total cumulative dose
Adult, should not exceed 400 mg/m² orally and 160 mg/m² by IV route.
Child, should not exceed 90 mg/m² by IV route.

Administration instructions
Solution for injection is red-orange
Give, over 10–15 minutes into side arm of a fast running sodium chloride 0.9% IV infusion.
Enous sclerosis may occur if the same vein is used for repeated cycles.
Anthracyclines are vesicant; avoid extravasation.

**Patient counselling**
Swallow capsules whole with a glass of water and a light meal; do not open or chew them.
Urine may appear red–orange for 1–2 days after dose.
Tell your doctor or nurse immediately if you feel any pain, stinging or burning during the injection or infusion.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

**Patient counseling**
Urine may appear red–orange for 1–2 days after dose.
Report immediately any pain, stinging or burning during injection or infusion.

**Practice points**
- some evidence that patients with ALL may be treated with a second course after recovery from toxicity
- monitor complete blood count, liver function and renal function at baseline and before each cycle
- monitor ECG and left ventricular ejection fraction at baseline and after every 3 cycles
- persistent QRS voltage reduction may indicate cardiotoxicity
- add up all doses of anthracycline to estimate cardiotoxic dosage limit
- scalp cooling to reduce hair follicle toxicity and subsequent loss during drug administration is controversial and may reduce drug transport, allowing the development of metastatic disease in the area.

**Products**
**IDARUBICIN VIAL 5 MG/VIAL (AS HCL) (ZAVEDOS®)**

**MITOMYCIN**
**Mode of action**
Reduced to active metabolite which cross links DNA, inhibits DNA, RNA and protein synthesis and may have an effect via free radical production.

**Indications**
Marketed: Palliation of stomach, pancreas, colon, lung, breast, cervix, head and neck, liver and bladder cancer.
Accepted: Anal carcinoma.

**Contraindications**
Bleeding disorders.
Uncontrolled infection.

**Specific considerations**
Renal impairment: Avoid use; may result in further decline in renal function.
Elderly: Reduced bone marrow reserve and age-related renal impairment result in increased adverse effects.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: Contraindicated.

**Adverse effects**
Common: myelosuppression, mild nausea and vomiting, stomatitis and alopecia.
Rare: haemolytic uraemic syndrome pulmonary fibrosis characterised by dyspnoea, nonproductive cough and radiographic evidence of pulmonary infiltrates; increased serum creatinine.
Myelosuppression: Cumulative, affecting mainly white cells and platelets. Nadir of white cell and platelet count occurs 4–6 weeks after a dose with recovery by about 8–10 weeks.
Extravasation: Extravasation may result in cellulitis, ulceration and sloughing, requiring excision and skin grafting.

**Dosage**
Consult specialist protocols. The following initial doses have been used: IV, 10–20 mg/m². Further doses depend on patient response and toxicity.
Intravesical, 10–40 mg once a week.

**Administration instructions**
Give as slow IV push into side arm of a fast running IV infusion of sodium chloride 0.9%, dilute further with
sodium chloride 0.9% and infuse over 30 minutes. Avoid extravasation
Due to highly irritant nature must not be given intrathecally, IM or SC. Solution for injection is light blue/purple
**Patient counselling**
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
It may also cause you to bruise and bleed more easily; tell your doctor if this occurs

**Practice points**
- monitor complete blood count and serum creatinine before each cycle and 6–8 weeks after the last dose
- cumulative toxicity may require stopping treatment
- bone marrow recovery may be delayed with subsequent courses
- corticosteroids have been used for pulmonary toxicity but therapeutic efficacy is not proven.

**Products**
**MITOMYCIN VIAL 5 MG/VIAL (MUTAMYCIN®)**

**MITOXANTRONE**

**Mode of action**
Cell cycle nonspecific action inhibiting DNA and DNA-dependent RNA synthesis by intercalation between base pairs with uncoiling of the helix. Interfere with topoisomerase II function, preventing re-ligation of DNA strand breaks. Peroxide and free radical production may also contribute to cytotoxicity. Anthracyclines also have immunosuppressive activity and mitoxantrone can induce apoptosis in leukaemic cells.

**Indications**
Marketed: Breast cancer; locally advanced or Metastatic; Non-Hodgkin's lymphoma; Acute myeloid leukaemia in adults, Chronic myeloid leukaemia in blast crisis.
Accepted: Acute lymphocytic leukaemia; Prostate cancer, refractory.

**Contraindications**
Maximal anthracycline exposure.
Cardiac toxicity from any anthracycline exposure
Intrathecal, IM or SC injection.

**Specific considerations**
Current radiotherapy: enhances skin and mucous membrane toxicity.
Recent radiotherapy in previous few weeks: radiation recall may occur.
Previous radiotherapy to chest region.
Cardiac disease, reduced cardiac reserve: cardiac toxicity may be enhanced.
Previous anthracycline exposure: cumulative cardiac toxicity; when calculating cumulative dose include any previous anthracyline exposure if changing to another anthracycline.
Treatment with trastuzumab: increases cardiotoxicity disproportionately to risk with individual anthracycline; avoid anthracyline for 22 weeks after trastuzumab and monitor cardiac function.
Elderly: Risk of increased myelosuppression
Hepatic impairment: Dose reduction required in moderate-to-severe impairment.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: Avoid use.

**Adverse effects**
Common: lassitude, stomatitis, oesophagitis, mild nausea and vomiting, partial or complete alopecia.
Infrequent: altered taste, GI bleeding, dyspnoea, rash, nail pigmentation, conjunctivitis.
Myelosuppression: Myelosuppression is common, affecting white cells, and to a lesser degree, platelets and red cells.
The white count nadir occurs about 10 days after a dose, with recovery by about 21 days.
Cardiac toxicity: May be acute or chronic: acute transient conduction abnormalities and arrhythmias are common; chronic cumulative dose-related damage to myofibrils reducing cardiac function starts about 1–6 months after initiation, may be irreversible and fatal.
 Mediastinal radiation, age <4 or >60 years, current administration of cardiotoxic agents and pre-existing cardiac disease increase the risk of cardiac toxicity.
Extravasation: Severe local tissue necrosis, severe cellulitis, thrombophlebitis or painful induration may result from extravasation. Liposomal formulations cause less local inflammation. Mitozantrone rarely causes necrosis. If extravasation is suspected, stop injection immediately, attempt to aspirate residual drug, institute extravasation treatment, resite IV access to another limb.
Secondary malignancies: Anthracycline use may be associated with later development of drug-resistant secondary
malignancies.

Dosage
Consult specialist protocols. The following initial doses have been used:
Single agent, IV 14 mg/m² for 1–5 days.
Combination therapy or debilitated patients, IV 10–12 mg/m² for 1–5 days.
Further courses depend on response and toxicity.
Total cumulative dose: 140 mg/m² or 100 mg/m² with predisposing risk factors such as previous anthracycline courses, mediastinal radiation or cardiac disease.

Administration instructions
Solution for injection is dark blue.
IV injection or by short infusion into side arm of a fast running sodium chloride 0.9% infusion. Venous sclerosis may occur if the same vein is used for repeated cycles.
Anthracyclines are vesicant; avoid extravasation.

Patient counseling
Urine and possibly whites of eyes and fingernails may appear blue–green for 1–2 days after dose.
Tell your doctor or nurse immediately if you feel any pain, stinging or burning during the injection or infusion.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

Practice points
- monitor complete blood count, liver function and renal function at baseline and before each cycle
- monitor ECG and left ventricular ejection fraction at baseline and after every 3 cycles
- persistent QRS voltage reduction may indicate cardiotoxicity
- add up all doses of anthracycline(s) to estimate cardiotoxic dosage limit
- scalp cooling to reduce hair follicle toxicity and subsequent loss during drug administration is controversial and may reduce drug transport, allowing the development of metastatic disease in the area.

Products
MITOXANTRONE VIAL 2 MG/VIAL (AS HCL)   10 ML VIAL (NOVANTRONE®, GENEFADRONR®, MITOXANTRON)

08.03.03 ANTIMETABOLITES

08.03.03.02 PURINE ANTAGONISTS

CLADRIBINE
Also known as chlorodeoxyadenosine, CdA or 2-CdA

Mode of action
Purine antimetabolite which inhibits DNA repair and synthesis, particularly in lymphocytes and monocytes.

Indications
Marketed: Hairy cell leukaemia, Chronic B-cell lymphocytic leukaemia (Leustatin®, second line after an alkylating agent has failed), Waldenström's macroglobulinaemia (Litak®, second line after an alkylating agent has failed).
Accepted: Non-Hodgkin's lymphoma.

Contraindications
Allergic reaction to the antimetabolite.

Specific considerations
Bone marrow depression: administration of cladribine may cause protracted and severe pancytopenia.
Pregnancy: Avoid use in pregnancy; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Common: fever, myelosuppression, prolonged depression (9–15 months) of helper/inducer (CD4, T4) cells (believed to contribute to depressed immune function), fatigue and headache, dizziness, weakness, insomnia, trunk pain, infection, mild nausea and vomiting, diarrhoea, constipation, abdominal pain, rash, pain and swelling at injection site, oedema, tachycardia, cough, myalgia, arthralgia.
Rare: neurotoxicity (doses used for hairy cell leukaemia), renal impairment (high doses), tumour lysis syndrome,
haemolytic anaemia, reversible increases in bilirubin and transaminases, pulmonary interstitial infiltrates. Fever: Fever, not due to infection, is very common, especially with first treatment course. Myelosuppression: Includes neutropenia, lymphopenia, anaemia and thrombocytopenia. Thrombocytopenia resolves approximately 12 days after a course of cladribine; neutropenia is generally mild with recovery after approximately 35 days; and recovery from anaemia occurs after approximately 56 days. Platelet recovery may be delayed with severe baseline thrombocytopenia.

**Dosage**
Consult specialist protocols. The following doses have been used.
- Hairy cell leukaemia: IV infusion, 90 micrograms/kg daily for 7 days. SC, 140 micrograms/kg daily for 5 days. IV infusion, 100 micrograms/kg daily for 7 days.
- Chronic lymphocytic leukaemia: IV infusion, 120 micrograms/kg (4.8 mg/m2) on days 1–5 of a 28 day cycle; give over 2 hours.
- Waldenström's macroglobulinaemia: SC, 100 micrograms/kg on days 1–5 of a 28 day cycle.

**Administration instructions**
IV infusion in 100–500 mL 0.9% sodium chloride over 2–24 hours.

**Patient counselling**
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur. Agents with myelosuppressant effects (not colaspase) This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

**Practice points**
- give a single course to treat hairy cell leukaemia
- give up to 6 courses for chronic lymphocytic leukaemia, depending on haematological tolerance; patients who fail to respond after 2 cycles are unlikely to respond
- experience in treating Waldenström's macroglobulinaemia is limited after 3 cycles
- monitor complete blood count at least each week during and after treatment and defer further therapy until haematological recovery has occurred
- fever occurs frequently in the first month and empiric anti-infective treatment should be used if clinically indicated.

**Products**
**CLADRIBINE VIAL 1 MG/VIAL (NOT REGISTERED)**

**FLUDARABINE**

**Mode of action**
Fludarabine phosphate is dephosphorylated to active fludarabine in serum. Fludarabine is a purine antimetabolite which inhibits synthesis of DNA.

**Indications**
Marketed: Chronic lymphocytic leukaemia.
Accepted: Acute leukaemia, Non-Hodgkin's lymphoma, Hairy cell leukaemia, Waldenström's macroglobulinaemia

**Contraindications**
Allergic reaction to the antimetabolite.

**Specific considerations**
Pre-existing neurological disorders: monitor closely for neurological adverse effects.
Treatment with cytarabine: fludarabine given first enhances the action of cytarabine; cytarabine given first inhibits fludarabine metabolic activation, reducing its efficacy.
Renal impairment: Reduce dose in mild impairment; do not use in moderate-to-severe impairment.
Elderly: Adjust dose for age-related renal impairment.
Pregnancy: Avoid use.; ADEC category D.
Breastfeeding: Avoid use.

**Adverse effects**
Common: myelosuppression, fever and chills, infection, moderate nausea and vomiting, diarrhoea, mucositis, constipation, malaise, paraesthesia, visual and hearing disturbances, insomnia, hyperglycaemia, oedema, maculopapular rash, itch, headache, elevated liver enzymes.
Infrequent: agitation, confusion, peripheral neuropathy, somnolence, GI bleeding, drug-induced interstitial pneumonitis (delayed effect occurring 3–28 days after repeated courses).
Rare: intestinal pseudo-obstruction, severe neurological effects (most frequently reported with high dose but may
occur with lower doses), autoimmune thrombocytopenia, autoimmune haemolytic anaemia, haemorrhagic cystitis, toxic epidermal necrolysis.

Myelosuppression: Includes neutropenia, thrombocytopenia and anaemia. Neutropenia nadir is approximately 13 days (range 3–25) after dose; platelet nadir is 16 days (range 2–32) after dose. Recovery usually occurs within 5–7 weeks provided there is no severe marrow failure due to replacement by disease. Cumulative myelosuppression may occur with multiple doses of fludarabine.

**Dosage**
Consult specialist protocols: the following initial dose has been used:
IV, 25 mg/m² daily for 5 days. Oral, 40 mg/m² daily for 5 days.
Repeat courses depend on patient response and toxicity.
Renal impairment: Halve dose in mild impairment.

**Administration instructions**
Give as IV injection or dilute to 100 mL with sodium chloride 0.9% and give over 30 minutes.

**Counselling**
Swallow tablets whole; do not break, crush or chew.
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

**Practice points**
- fludarabine has produced some response when used in non-Hodgkin’s lymphoma and hairy cell leukaemia and is used with cytarabine in some protocols for acute myeloid leukaemia
- monitor closely for haemolysis which can be a late complication
- monitor complete blood count, liver and renal function before each course of fludarabine; observe frequently for signs of infection
- observe closely for signs of neurological adverse effects; visual changes are an indication of neurotoxicity
- Repeated low dose schedules appear to cause less neurotoxicity than an equivalent single high dose.
- men and women should use adequate contraception during, and for at least 6 months after, fludarabine therapy

**Products**
FLUDARABINE VIAL 50 MG/VIAL (AS PHOSPHATE) (FLUDARA®)

**MERCAPTOPURINE**

**Mode of action**
Impairs cellular proliferation through interference with purine synthesis. Active metabolite of azathioprine. Cross-resistance with thioguanine occurs.

**Indications**
Marketed: Acute lymphoblastic leukaemia, Acute and chronic myeloid leukaemia
Accepted: Inflammatory bowel disease.

**Contraindications**
Porphyria; Allergic reaction to the antimetabolite.

**Specific considerations**
Renal impairment: Dose reduction may be required.
Hepatic impairment: Use with caution; monitor liver function tests.
Pregnancy: Avoid use; ADEC category D.
Breastfeeding: Avoid use.

**Adverse effects**
Common: mucositis, myelosuppression (dose-dependent), cholestatic jaundice (may be reversible, but may progress to hepatic necrosis with continued treatment; onset is more common with daily doses >2.5 mg/kg).
Rare: drug fever, GI ulceration, pancreatitis, dry, scaly rash, alopecia, rash, arthralgia, facial oedema, secondary leukaemia, myelodysplasia.

**Dosage**
Consult specialist protocols; the following doses have been used:
Antineoplastic: Initially 2.5 mg/kg once daily. Maintenance doses or further courses depend upon patient response and toxicity. Dose may be calculated using body surface area rather than weight.
Inflammatory bowel disease: 1.5–2 mg/kg once daily.
Patient counseling
Swallow tablets whole; do not crush or chew.
Stop taking this medicine and contact your doctor if you develop yellowing of the skin, dark urine or pale stools.
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

Practice points
- 1 in 300 patients lack functional thiopurine methyltransferase activity and are at risk of severe
  myelosuppression unless the dose is drastically reduced; these patients may tolerate doses one-tenth of
  normal or less
- round dosage to the nearest 25 mg
- monitor complete blood count and liver function tests each week for the first month of treatment, then each
  month once stable.

Products
MERCAPTOPURIN TABS 50 MG (PURINETHOL®)

THIOGUANINE
Also known as tioguanine 6-TG.

Mode of action
Purine antimetabolite with activity similar to mercaptopurine; cross resistance with mercaptopurine occurs.

Indications
Acute myeloid leukaemia
Chronic myeloid leukaemia

Contraindications
Allergic reaction to the antimetabolite.

Specific considerations
Treatment with busulfan: combination with thioguanine may cause hepatotoxicity; avoid combination.
Renal impairment: Consider dosage reduction in severe impairment; titrate daily dose to desired haematological
  effects.
Hepatic impairment: Consider dosage reduction in severe impairment; titrate daily dose to desired haematological
  effects.
Pregnancy: Avoid use in pregnancy unless benefits outweigh risks; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Common: myelosuppression, veno-occlusive hepatic disease (short term cyclical therapy), mild nausea and vomiting,
  stomatitis, diarrhoea, hyperuricaemia.
Infrequent: jaundice, elevation of liver enzymes (combination therapy), rash, peripheral neuropathy.
Rare: intestinal necrosis and perforation.
Myelosuppression: Neutropenia usually occurs 2–4 weeks after a dose, but may occur earlier. Thrombocytopenia
  also occurs.

Dosage
Consult specialist protocols; it is usually used with other antineoplastic agents. The following initial dose has been
  used; further treatment depends upon patient response and toxicity.
100 mg/m² daily in divided doses.

Patient counselling
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your
doctor what to do if you think you may be getting one.

Practice points
- metabolism of thioguanine is not dependent on xanthine oxidase, so usual doses may be given with
  allopurinol
- monitor complete blood count each week during single agent therapy or more frequently during
  combination therapy; stop treatment if there is an abnormally rapid decrease in blood count, unless
  induction of bone marrow hypoplasia is desired
• monitor liver function tests each week and serum creatinine each month during therapy
• long term maintenance treatment not recommended; higher risk of liver toxicity reported (e.g. veno-occlusive hepatic disease, portal hypertension), particularly in children; usually reversible on stopping treatment
• thioguanine has poor and highly variable oral bioavailability.

Products
TIOGUANINE TABS 40 MG (LANVIS®)

08.03.03 PRIMIDONE ANTAGONISTS

CAPECITABINE

Mode of action
Pro-drug of fluorouracil. Converted to fluorouracil by a 3-step conversion process in which the final step is more active in malignant than normal cells.

Indications
Breast cancer, after failure of taxanes and an anthracycline, or if standard agents are contraindicated
Breast cancer (with docetaxel) after failure with an anthracycline
Colorectal cancer, advanced or metastatic

Contraindications
Allergy or contraindication to fluorouracil.
Allergic reaction to the antimetabolite

Specific considerations
History of coronary artery disease: possible increased risk of MI, angina, ECG changes, cardiogenic shock, sudden death.
Renal impairment: Avoid use in moderate-to-severe impairment.
Hepatic impairment: No initial dose reduction is necessary in mild-to-moderate hepatic dysfunction. There are no studies of use in severe impairment.
Pregnancy: Avoid use in pregnancy unless benefits outweigh risks; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Common: diarrhoea, mild nausea and vomiting, anorexia, flatulence, stomatitis, constipation, dyspepsia, 'hand-foot' syndrome (peripheral numbness, paraesthesia, erythema, swelling and blistering), weakness, fatigue, abdominal pain, increased ALP, transaminases and serum creatinine, hyperbilirubinaemia, taste disturbance, insomnia, dizziness, headache, dry skin, rash, dry mouth, skin pigmentation, conjunctivitis, nail disorders.
Infrequent: pyrexia, oesophagitis, duodenitis, colitis, GI haemorrhage, encephalopathy, confusion, cerebellar signs, cardiac chest pain, photosensitivity reaction, radiation recall.

Dosage
Consult specialist protocols. The following initial dose has been used as a single agent or in combination therapy.
Breast cancer: Oral, 2500 mg/m2 daily in 2 divided doses every 12 hours for 14 days of a 21-day cycle. Further courses depend on patient response and toxicity.

Patient counseling
Swallow whole; do not break, chew or crush the tablets. Take within 30 minutes after the end of a meal.
Tell your doctor if you develop diarrhoea or numbness, tingling, pain or swelling of hands or feet as you may require treatment.
Avoid excessive sun exposure of skin, wear protective clothing and use sunscreen.
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

Practice points
• symptoms of 'hand-foot' syndrome may be alleviated by pyridoxine 25–50 mg daily; stop capecitabine temporarily; mild emollients or creams may help
• diarrhoea may be dose-limiting; stop capecitabine and consider fluid and electrolyte replacement; loperamide 4 mg initially and 2 mg every 2 hours may be effective
monitor hepatic function tests at baseline and at least every cycle; interrupt treatment until bilirubin concentration is <3 times the upper limit of normal or aminotransferase concentration is <2.5 times the upper limit of normal

monitor complete blood count and serum creatinine before each course of capecitabine
dihydropyrimidine dehydrogenase deficiency (DPD) is a contraindication for capecitabine in the US.

Products
CAPECITAPINE TABS 500 MG (XELODA®)

CYTARABINE
Mode of action
Antimetabolites inhibit DNA and RNA synthesis by interfering with purine or pyrimidine metabolic pathways. Methotrexate and raltitrexed are folate antagonists and interfere with nucleotide synthesis. Most antimetabolites act on dividing cells but some, e.g. cladribine, affect resting and proliferating cells.

Indications
Marketed:
Acute myeloid leukaemia (main indication).
Acute lymphoblastic leukaemia
Chronic myeloid leukaemia (blastic phase)
Non-Hodgkin's lymphoma.
Meningeal involvement by leukaemia
Accepted: Mobilisation of haemopoietic stem cells for subsequent infusion after myeloablative or myelosuppressive chemotherapy.

Contraindications
Allergic reaction to the antimetabolite.

Specific considerations
Treatment with fludarabine: fludarabine given first enhances the action of cytarabine; cytarabine given first inhibits fludarabine metabolic activation, reducing its efficacy.
Hepatic impairment: Lower doses are required in severe impairment.
Pregnancy: Avoid use; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
A syndrome of bone and muscle pain, fever, malaise, conjunctivitis and rash may occur 6–12 hours after administration and may respond to corticosteroids.
Common: myelosuppression moderate nausea and vomiting, diarrhoea, mucositis, conjunctivitis, local pain, cellulitis and thrombophlebitis at site of injection, alopecia, hyperuricaemia, keratoconjunctivitis (high doses).
Infrequent: GI haemorrhage, oesophagitis, jaundice and elevated bilirubin, transaminases and ALP concentrations, rash, fever, dizziness; vein staining and hyperpigmentation (with continuous infusions).
Rare: chest pain, urinary retention, anaphylaxis, renal impairment.
Myelosuppression: Major adverse effect, includes neutropenia, thrombocytopenia and anaemia; more severe after high doses or continuous infusions. Neutropenia nadir is 7–9 days after dose; thrombocytopenia nadir is 12–15 days after dose. Cytarabine is usually given with other antineoplastic agents and high dose treatment usually results in severe pancytopenia for about 2 weeks. Intensive supportive care for sepsis and haemorrhage is usually required.
Other
High dose: severe and sometimes fatal GI and pulmonary toxicity, CNS toxicity, e.g. coma, somnolence, personality changes (usually reversible), cardiomyopathy, peripheral neuropathy; haemorrhagic conjunctivitis and keratitis can occur (prophylactic corticosteroid, sympathomimetic or lubricant eye drops may help).
Intrathecal: systemic toxicity may occur, usually with higher doses and more frequent administration; common adverse effects include mild nausea, vomiting, fever, myelosuppression and transient headache; rare effects include meningism, paraesthesia, paraplegia, seizures.

Dosage
Consult specialist protocols. Usually given in combination therapy.

Administration instructions
May be given by SC, IV and intrathecal (IT) injection, and by IV infusion.
Use solutions of 100 mg/mL for IT injection; must be further diluted to a maximum of 10 mL.
Patient counselling
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

Practice points
- monitor complete blood count, renal and hepatic function before, and at frequent intervals during, treatment
- observe closely for signs of neurologic toxicity in patients receiving high dose cytarabine; rapid infusion may increase neurotoxic effects.

Products
CYTARABINE VIAL 100 MG/VIAL (POWDER FOR INJECTION) (ALEXAN®, CYTARABINE®, CYTOSAR®)

CYTARABINE VIAL 500 MG/VIAL (POWDER FOR INJECTION) (CYTARABINE®, CYTOSAR®)

FLUOROURACIL
Also known as 5-fluorouracil or 5-FU.

Mode of action
Pyrimidine antimetabolite which interferes with synthesis of DNA and RNA

Indications
Palliative treatment of solid tumours including breast, colon, liver, rectum, stomach, head and neck, bladder, pancreas, gall bladder.
Chemoradiotherapy after surgery for adenocarcinoma of stomach or gastro-oesophageal junction
Solar and senile keratoses and Bowen's disease (topical)

Contraindications
Porphyria.
Allergic reaction to the antimetabolite.

Specific considerations
Pre-existing heart disease: may increase risk of arrhythmia.
Treatment with paclitaxel: pretreatment with fluorouracil may inhibit cytotoxic action of paclitaxel; avoid combination.
Surgery: Do not use within 1 month of major surgery.
Pregnancy: Avoid use in pregnancy unless benefits outweigh risks; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Adverse effects differ depending on whether fluorouracil is given as bolus doses or continuous infusion.
Myelotoxicity is common with bolus doses but unusual with continuous infusion. 'Hand-foot' syndrome, is common with continuous infusion.
Common: myelosuppression, GI effects including mild nausea and vomiting, stomatitis, diarrhoea (more severe when fluorouracil is given with calcium folinate), alopecia, itch, maculopapular rash.
Infrequent: oesophagitis, GI ulceration and bleeding, proctitis, 'hand-foot' syndrome (red, flaking rash with painful, swollen hands and feet), photosensitivity, confusion, ataxia, nystagmus, headache, acute cerebellar syndrome, lacrimation, visual changes, photophobia.
Rare: myocardial ischaemia, arrhythmias, ventricular tachycardia, anaphylaxis and allergic reactions, fever without signs of infection, vein pigmentation, multifocal inflammatory leucoencephalopathy.

Myelosuppression: Includes neutropenia, thrombocytopenia and anaemia. Neutropenia nadir occurs at 9–14 days but may be as late as 25 days after the first course. Platelet nadir occurs about 7–17 days after a dose, with recovery after about a further 10 days.

Multifocal inflammatory leucoencephalopathy: Is associated with combined treatment with levamisole; symptoms include memory loss, confusion, paraesthesia, muscle weakness, speech disturbances, coma and seizures; may be partly reversible if both drugs stopped and corticosteroids given.
Topical use: Local pain, itch, pigmentation, burning, dermatitis, scarring.

Dosage
Systemic uses
Consult specialist protocols; doses vary depending on tumour type.
Topical uses
Apply cream 1–2 times daily, usually for 3–4 weeks at first. Bowen's disease also requires an occlusive dressing (not usually needed for solar or senile keratoses).

**Administration instructions**
Give IV, by slow injection or infusion in sodium chloride 0.9% or glucose 5% over 4 hours or by continuous infusion over 24 hours or longer.

**Patient counselling**
Avoid excessive or prolonged sun exposure, wear protective clothing and use sunscreen. Topical, apply a thin layer to affected area using a non-metal applicator or rubber gloves. Avoid contact with your eyes and mouth. Your skin may redden, blister, peel or crack where you apply this medicine; this is to be expected. This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur. Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

**Practice points**
- obtain complete blood count before each course
- avoid excessive or prolonged sun exposure
- stop infusion immediately if chest pain or cardiogenic shock occurs
- stop treatment if painful red hands or feet occur; pyridoxine 25–50 mg daily may help; mild emollients or creams may also be used; restart treatment at a lower dose
- diarrhoea may be dose limiting; use loperamide 4 mg initially and 2 mg every 2 hours until it settles; consider hydration and electrolyte replacement
- when used with folinic acid for metastatic colorectal cancer response rates and toxicity are increased; response rates (hence improvement in symptoms) may be altered by different injection rates, but the optimum sequence and timing has not been established
- use an occlusive dressing for keratosis palmaris but not for solar or senile keratoses.

**Products**
- FLUOROURACIL VIAL 1000 MG/VIAL 20 ML VIAL (5-FLUOROURACIL®)
- FLUOROURACIL VIAL/AMP 500 MG/VIAL/AMP 10 ML VIAL/AMP (5-FLUOROURACIL®, FIVOFLU®)

**GEMCITABINE**
**Mode of action**
Pyrimidine antimetabolite chemically related to cytarabine. Gemcitabine is metabolised intracellularly to active nucleosides which inhibit DNA synthesis and induce apoptosis.

**Indications**
Marketed:
- Non–small cell lung cancer, locally advanced or metastatic
- Pancreatic adenocarcinoma, locally advanced or metastatic
- Pancreatic cancer refractory to fluorouracil.
- Bladder cancer, alone or with cisplatin
- Breast cancer, unresectable, locally recurrent or metastatic following adjuvant or neoadjuvant chemotherapy, use with paclitaxel
- Ovarian cancer, recurrent following >6 months platinum-based chemotherapy, use with carboplatin.
- Accepted:
  - Chronic lymphocytic leukaemia
  - Non-Hodgkin's and mantle cell lymphoma.
  - Hodgkin's disease

**Contraindications**
Allergic reaction to the antimetabolite

**Specific considerations**
Radiotherapy within 7 days of gemcitabine: increases risk of radiation injury; may need to reduce dose of gemcitabine and/or radiation, seek specialist advice.
Hepatitis, cirrhosis or liver metastases: gemcitabine may worsen liver function.
Hepatic impairment
Increased toxicity in patients with elevated bilirubin; dose reduction is recommended.
Pregnancy: Avoid use in pregnancy; ADEC category D.
Breastfeeding: Avoid use.

**Adverse effects**
Common: myelosuppression, increases in hepatic enzymes and bilirubin, stomatitis, mild nausea and vomiting, diarrhoea, constipation; mild proteinuria and haematuria, (mild and usually not associated with changes in serum creatinine), flu-like symptoms (eg. fever, headache, back pain, chills, myalgia, anorexia, cough, rhinitis, sweating, malaise), insomnia or somnolence; dyspnœa; peripheral oedema; alopecia, rash, itch.
Infrequent: pulmonary toxicity.
Rare: renal failure, haemolytic uraemic syndrome, skin reaction (including desquamation, vesiculation, ulceration), anaphylactoid reaction, facial oedema, adult respiratory distress syndrome, MI, heart failure, arrhythmia, hypotension.

**Myelosuppression:** Includes usually mild and transient neutropenia, thrombocytopenia and anaemia. Nadir 7–14 days after dose with recovery after 22–24 days.

**Pulmonary toxicity:** Interstitial pneumonitis affects <1% of patients; severe, sometimes fatal, interstitial pneumonitis, pulmonary oedema, bronchospasm and adult respiratory distress syndrome reported. Stop treatment, corticosteroids may relieve symptoms.

**Dosage**
Consult specialist protocols.

**Administration instructions**
Give as IV infusion in 0.9% sodium chloride over 30 minutes.

**Patient counselling**
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur. Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

**Practice points**
- monitor hepatic and renal function before each cycle of chemotherapy
- monitor complete blood count before each dose of gemcitabine.

**Products**
**GEMCITABINE VIAL 1 GM/VIAL (AS HCL) (GEMEZAR®)**

**08.03.04 Others**

**COLASPASE (L-ASPARAGINASE)**
Another source of asparaginase is Erwinia chrysanthemi.

**Mode of action**
Catalyses the conversion of the amino acid L-asparagine to aspartic acid and thereby reduces the availability of L-asparagine to leukaemic cells. Unlike normal cells, certain types of leukaemic cells do not synthesise L-asparagine, which is essential for cell growth and survival.

**Indications**
Acute lymphoblastic leukaemia
Some subtypes of non-Hodgkin's lymphoma.

**Contraindications**
History of pancreatitis
Allergic reaction to the antimetabolite

**Specific considerations**
Adults: adverse effects are usually more severe in adults than in children.
Treatment with methotrexate: colaspase, given just before methotrexate, reduces its effect; give colaspase 9–10 days before or just after methotrexate.
Pregnancy: Avoid use; ADEC category D.
Breastfeeding: Avoid use.

**Adverse effects**
Common: allergic reactions, mild nausea and vomiting, fatty changes in the liver, hypertriglyceridaemia, elevated transaminases, bilirubin, albumin and calcium concentrations, prolonged clotting times, increased fibrin degradation products, reduced fibrinogen, uremia (usually prerenal), pancreatitis, hyperuricaemia.
Infrequent: transient proteinuria, hyperglycaemia (rarely leading to diabetic ketoacidosis and death), CNS effects
including depression or hyperexcitability, chills and fever (possibly caused by bacterial endotoxins in the preparation).
Rare: intracranial haemorrhage or thrombosis, peripheral venous and arterial thrombosis, transient myelosuppression, acute renal failure, parkinsonian-like syndrome, diarrhoea, oral ulceration, alopecia.
Allergic reactions
Include immunologically related bleeding and thrombotic events; other organ systems including CNS, liver and pancreas are also affected.
Anaphylaxis is more frequent after repeated courses but may occur after initial administration, including test dose.

**Dosage**
Doses relate to colaspase and are expressed here in Kyowa units (KU); they may not be identical with other doses expressed in international units. Other forms of asparaginase are not interchangeable with colaspase.
Consult specialist protocols for information on test doses and dose regimens.
A test dose should always be given at the start of a treatment course.
Test dose, SC, 1–10 KU in 0.1 mL water for injection.
Initial dose, IM/IV, 50–200 KU/kg daily or on alternate days has been used in combination treatment. Further courses depend on patient response and toxicity.

**Administration instructions**
IV infusion in 200–500 mL of sodium chloride 0.9% or glucose 5% over 2–4 hours
IM injection in 2–4 mL sodium chloride 0.9%

**Patient counseling**
Allergic reactions to colaspase such as joint pain, puffy face, rash, itching, stomach cramps and breathing difficulties occur frequently, especially if the course is repeated. Tell your doctor immediately if any of these reactions occur.
This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

**Practice points**
- monitor liver and renal function, INR, serum amylase and blood glucose every second day
- resuscitation equipment must be available; a negative reaction to the test dose does not preclude an allergic reaction
- patients who develop allergic reactions can sometimes be treated with Erwinia-derived asparaginase: use extreme caution in such individuals
- usually used with other drugs such as vincristine, prednisolone and daunorubicin
- colaspase increases risk of hyperglycaemia with prednisolone; monitor blood glucose
- colaspase is a contact irritant; avoid contact with skin or mucous membranes; if contact occurs, flush area with running water for 15 minutes.

**Products**
COLASPASE (L-ASPARAGINASE) POWDER FOR INJECTION 10,000 IU/VIAL (ASPARGINASE®)

**HYDROXYUREA**
Also known as hydroxycarbamide

**Mode of action**
Inhibits DNA synthesis by interfering with the conversion of ribonucleotides to deoxyribonucleotides

**Indications**
Marketed: Chronic myeloid leukaemia, Melanoma, Ovarian cancer, recurrent, metastatic or inoperable
Accepted: Adenocarcinoma of cervix, Essential thrombocythaemia, Polycythaemia vera, Sickle cell anaemia (prophylaxis against crisis), Squamous cell carcinoma of head and neck.

**Contraindications**
Allergic reaction to the antimetabolite

**Specific considerations**
Renal impairment: Reduce dose, seek specialist advice.
Pregnancy: Avoid use in pregnancy; ADEC category D.
Breastfeeding: Avoid use.

**Adverse effects**
Common: myelosuppression, haemolysis, anorexia, stomatitis, mild nausea and vomiting, constipation, diarrhoea, maculopapular rash, facial erythema, itch.
Infrequent: hyperpigmentation, atrophy of skin and nails, cutaneous leg ulcers.
Rare: alopecia, skin cancer, dysuria, elevated serum creatinine, fever, chills, malaise, oedema, elevation of liver enzymes, acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnoea.
Myelosuppression: Dose dependent. White cell nadir is 7–14 days after a dose with marrow recovery at 14–21 days. Peripheral blood count usually recovers rapidly when therapy stops but, rarely, persistent myelosuppression may occur.
Other: Visual and auditory hallucinations and haematological toxicity reported in patients with moderate-to-severe renal impairment.

Dosage
Consult specialist protocols
The following initial doses have been used.
80 mg/kg as a single dose every third day or 20–30 mg/kg daily. Further courses depend on response and toxicity.

Patient counselling
If you are unable to swallow the capsules they can be carefully opened and the contents mixed with a glass of water. Drink it immediately. Don't worry if some of the powder from the capsule floats to the surface. This medicine may cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur. Agents with myelosuppressant effects (not colaspase)
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

Practice points
- monitor complete blood count at baseline and each week until stabilisation, then every 4–8 weeks during chronic therapy (macrocytosis is a normal consequence of the action of hydroxyurea and is not a toxic complication)
- monitor renal and liver function at baseline and regularly during chronic therapy
- treat stomatitis with benzydamine mouthwash and oral analgesics, eg paracetamol

Products
HYDROXYUREA CAPS 500 MG (HYDREA®)

08.03.04 ANTINEOPLASTIC ANTIBODIES

RITUXIMAB

Mode of action
A chimeric anti-CD20 monoclonal antibody which binds to antigen CD20 located on B lymphocytes and initiates an immune response which lyses normal and malignant B cells. Apoptosis is also induced. Regeneration of normal B lymphocytes occurs.

Indications
B cell non-Hodgkin's lymphoma (NHL), CD20-positive
- relapsed or refractory low grade or follicular
- untreated stage III/IV follicular (plus chemotherapy)
- diffuse large B cell (plus chemotherapy)

Contraindications
Allergy to rituximab.
Hypersensitivity to murine proteins.

Specific considerations
Heart cardiac disease: increases risk of angina or cardiac arrhythmia.
Large tumour burden: increased risk of severe tumour lysis syndrome.
Pulmonary disease or lung metastases: increases risk of severe dyspnoea, bronchospasm and hypoxia.
Hepatitis B carriers: risk of reactivation of hepatitis; monitor for clinical and laboratory signs of infection and of hepatitis during treatment and for several months after it.
Breasfeeding: No data available.

Adverse effects
Adverse reactions are less frequent with subsequent doses
Common: anaphylaxis (shortly after beginning infusion), infusion-related symptoms, cytokine release syndrome.
Infrequent: neutropenia (late in onset, occurs rarely), anaemia, thrombocytopenia, angina, MI, ventricular fibrillation.
Rare: haemolytic anaemia, aplastic anaemia, severe skin conditions days to months after treatment (including Stevens–Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis), pulmonary infiltrates, interstitial pneumonitis, cranial neuropathy (vision or hearing loss).

Infusion-related symptoms: Occur 30–120 minutes after starting infusion and include fever, chills and/or rigors, nausea, vomiting, urticaria, itch, headache, bronchospasm, dyspnoea, angioedema, rhinitis, hypotension.

Cytokine release syndrome: Occurs 1–2 hours or longer after starting infusion; includes dyspnoea, bronchospasm and hypoxia; usually associated with tumour lysis syndrome which may occur 12–24 hours after completing initial infusion.

Lymphocytopenia: Rapid and sustained loss of B lymphocytes from peripheral blood occurs after administration of rituximab. Gradual recovery of lymphocytes occurs approximately 6 months after completion of treatment.

**Dosage**

Use the same dosage as a single agent or with chemotherapy. Consult specialist protocols. The following initial doses have been used. Further courses depend on patient response and toxicity.

- **IV infusion 375 mg/m²**
  - Low grade or follicular NHL, monotherapy, give once weekly for 4 doses. Combination therapy, give on the first day of each chemotherapy cycle for 8 cycles.
  - Diffuse large cell NHL, give on the first day of each chemotherapy cycle.

**Administration instructions**

- Dilute required dose with sodium chloride 0.9% or glucose 5%.
- Initial rate 50 mg/hour, increasing rate by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour. Subsequent infusions may be started at 100 mg/hour, increasing to 400 mg/hour if tolerated.
- Use a slower infusion rate for patients with high tumour burden, e.g. >25 000 cells/mm³.

**Patient counseling**

Tell your doctor or nurse immediately if you get fever, chills, rash, difficulty breathing or swollen lips, tongue or face.

**Practice points**

- Premedicate with paracetamol, an antihistamine, e.g. promethazine, and possibly a corticosteroid, such as dexamethasone, 30–60 minutes before each dose
- Emergency treatment for anaphylaxis (adrenaline, antihistamine and corticosteroid) must be readily available
- Observe patient for infusion-related symptoms and stop or slow the infusion rate if they occur; restart the infusion at half the previous rate when symptoms abate
- If severe cytokine release syndrome develops, stop infusion and treat symptomatically
- Consider withholding antihypertensive medication for 24 hours to prevent hypotension
- Continue monitoring for at least 2 hours after infusion is completed
- Monitor complete blood count before each course of rituximab
- Screen for hepatitis B before starting rituximab as treatment may reactivate infection; continue to monitor for signs of infection during, and for several months after, treatment; stop rituximab if hepatitis develops.

**Products**

- RITUXIMAB VIAL 100 MG/VIAL 10 ML VIAL (MABHERA®)
- RITUXIMAB VIAL 500 MG/VIAL 50 ML VIAL (MABHERA®)

**TRASTUZUMAB**

**Mode of action**

Recombinant humanised monoclonal antibody that binds to human epidermal growth factor receptor 2 (HER2), thereby inhibiting the proliferation of tumour cells that over-express HER2.

**Indications**

Metastatic breast cancer that over-expresses HER2:
- Untreated disease (combined with a taxane)
- Prior chemotherapy for this disease (monotherapy)

**Contraindications**

Allergy to trastuzumab.

**Specific considerations**

Heart disease: increases risk of cardiac dysfunction.
Dyspnoea due to advanced malignancy: increases risk of respiratory distress or fatal infusion reaction.
Treatment with anthracyclines: increases cardiotoxicity disproportionately to risk with individual anthracycline;
avoid anthracycline for 22 weeks after trastuzumab and monitor cardiac function.
Elderly: Risk of cardiac dysfunction may be increased.
Pregnancy: Avoid use in pregnancy unless benefit outweighs risk; ADEC category B2.
Breastfeeding: No data available.

Adverse effects
Common: moderate-to-severe heart failure and reduced ejection fraction, cough, wheezing, bronchospasm, paroxysmal nocturnal dyspnoea, pleural effusion, peripheral oedema, maculopapular rash, hepatic toxicity (ascites, hepatitis), infusion-related symptoms.
Infrequent: hypersensitivity
Rare: acute respiratory distress syndrome, pulmonary fibrosis (pulmonary infiltrates may be delayed in onset).
Infusion-related symptoms
Include chills, fever, weakness, pain, nausea, vomiting, headache, hypotension, hypertension.

Dosage
The same dose of trastuzumab is used for monotherapy and combination treatment. Consult specialist protocols.
Repeat dosing depends on patient response and toxicity.
IV infusion 4 mg/kg as initial dose, then 2 mg/kg once a week

Administration instructions
Infuse in 250 mL of 0.9% sodium chloride over 90 minutes for initial dose. If the initial dose is well tolerated give subsequent doses over 30 minutes.

Patient counseling
Tell your doctor or nurse immediately if you get fever, chills, rash, difficulty breathing, chest pain or severe swelling of your feet or legs.

Practice points
• emergency treatment (adrenaline, antihistamine and corticosteroid) for anaphylaxis must be readily available
• observe patient for infusion-related symptoms and stop or slow the infusion rate if symptoms occur; restart the infusion at half the previous dose when symptoms abate
• monitor cardiac status of all patients before starting trastuzumab, including history and physical examination, ECG, echocardiogram and measurement of ejection fraction
• continue to monitor cardiac function every 3 months (or more frequently) and consider risk-benefit of continuing trastuzumab if left ventricular function decreases
• trastuzumab therapy may continue during periods of reversible taxane-induced myelosuppression

Products
TRASTUZUMAB VIAL 440 MG/VIAL (HERCEPTIN®)

08.03.5 TYROCINE KINASE INHIBITORS

IMATINIB
Also known as STI571

Mode of action
Tyrosine kinase inhibitor which reduces proliferation and primarily induces apoptosis in cells with abnormalities including Philadelphia chromosomal, platelet derived growth factor receptor (PDGFR) or c-kit tyrosine kinase (e.g. chronic myeloid leukaemia, GI stromal tumours).

Indications
Chronic myeloid leukaemia (CML).
GI stromal tumours.

Specific considerations
Elderly: severe fluid retention is more common
Pregnancy: Do not use; ADEC category D.
Breastfeeding: Avoid use.

Adverse effects
Common: myelosuppression, nausea and vomiting, diarrhoea, severe fluid retention (eg pleural effusion, pericardial effusion, ascites, periortbit and lower limb oedema), muscle cramp, increased bilirubin or transaminases, rash, arthralgia, GI bleeding, dyspnoea
Infrequent: heart failure, pulmonary oedema, renal failure, gynaecomastia
Rare: angioedema, Stevens–Johnson syndrome, Sweet's syndrome
Myelosuppression: Neutropenia and thrombocytopenia are common; neutropenia lasts 2–3 weeks and thrombocytopenia 3–4 weeks. Cytopenias are more common in blast and accelerated phase of CML.

Dosage
Consult specialist protocols. The following initial doses have been used. Further courses depend on patient response and toxicity.
CML, chronic phase: Adult, 400–600 mg once daily. Child >3 years, 260 mg/m2 once daily (maximum 400 mg).
CML, accelerated phase or blast crisis: Adult, 600–800 mg daily. Give 800 mg dose as 400 mg twice daily.
Child >3 years, 340 mg/m2 daily (maximum 600 mg). Daily dose may be given in 2 divided doses, morning and evening.
GI stromal tumours: 400–600 mg daily.

Patient counseling
Take with food and a large glass of water to avoid stomach upset. Alternatively, put the tablets in a glass of water or apple juice, stir until they disintegrate, then drink it straight away; rinse glass and drink this too.
Weigh yourself twice a week and tell your doctor if your weight increases by more than 1–2 kg in a week.

Practice points
- monitor complete blood count before starting and each week for the first month, every other week for the second month and then every 2–3 months
- measure liver function at baseline, then every month, or as clinically indicated; delay treatment or reduce dose if severe hepatotoxicity occurs
- monitor regularly for signs and symptoms of fluid retention

Products
IMATINIB TABS 100 MG (AS MESILATE) (GLIVEC®)

08.03.6. PLATINUM COMPOUNDS

CARBOPLATIN

Mode of action
Platinum compounds are activated within the cell by displacement of chloride ions, leaving positively charged platinum molecules which react with DNA. DNA replication, transcription and cell division are inhibited, ultimately inducing apoptosis. Other mechanisms may also be involved. Platinum compounds are cell cycle nonspecific.

Indications
Marketed: Treatment of advanced ovarian carcinoma of epithelial origin, alone and in combination regimens.
Accepted: Non–small cell and small cell lung cancer, Alternative to cisplatin for head and neck cancer, Alternative to standard preferred regimens for Wilms' tumour, Adjuvant therapy in some brain tumours, e.g. medulloblastoma, Non-Hodgkin's lymphoma (salvage therapy).

Specific considerations
Allergic reaction to a platinum compound: cross-sensitivity is not absolute; if necessary, try an alternative platinum compound (with appropriate precautions).
Treatment with other nephrotoxic drugs: additive risk of nephrotoxicity; use with caution (avoid with cisplatin).
Exposure, eg industrial, to other platinum compounds: may produce an allergic reaction to cisplatin or carboplatin.
Renal impairment: Adjust dose by Calvert's formula (see Dosage) based on creatinine clearance or measure glomerular filtration rate. Myelosuppression is more severe in renal impairment.
Elderly: Dosage reduction due to age-related renal impairment may be required. Peripheral neuropathy is reported more often.
Children: Carboplatin has been used for brain tumour (from 6 months of age) and Wilms' tumour (2–15 years). Adverse effects are similar to those in adults. Cisplatin has also been used to a limited extent in childhood tumours. Otoxicity may be more severe in children. Oxaliplatin has not been used.
Pregnancy: Avoid use; ADEC category D.
Breastfeeding: Insufficient data; avoid use.

Adverse effects
Common: myelosuppression, moderate nausea and vomiting, peripheral neuropathy, taste abnormality, fatigue, reversible elevation of serum creatinine, mild and reversible electrolyte abnormalities (hyponatraemia, hypokalaemia, hypocalcaemia, hypomagnesaemia); mild elevations of ALP, liver transaminases and bilirubin; alopecia, myalgia, arthralgia, weakness.
Infrequent: otoxicity, GI pain, diarrhoea, constipation, mucositis.
Rare: haemolytic uraemic syndrome, loss of vision (at higher than usually recommended doses).
Myelosuppression: Occurs frequently, especially in patients receiving combination regimens. Nadir of platelet and neutrophil counts occurs 14–21 days after a dose, with recovery usually within 28 days. Anaemia may be cumulative, requiring transfusions in patients receiving prolonged (e.g. 4–6 cycles) therapy.

**Dosage**
Consult specialist protocols. The Calvert formula is commonly used for carboplatin dosing:

Total dose (mg) = target AUC x [GFR+25]  
AUC = area under the curve [(mg/mL] x minute).  
GFR = glomerular filtration rate, (mL/minute), approximately equivalent to calculated creatinine clearance.  
Target AUC is 6 mg/mL x minute for patients who have not received previous chemotherapy and where carboplatin is used in combination, or 7 mg/mL x minute if carboplatin is used alone.  
Target AUC is 5 mg/mL x minute for previously treated patients.  
Note dose calculated is given in mg not mg/m².  
This formula should not be used in children or adults with severe renal impairment.

**Administration instructions**
Do not prepare or administer with equipment containing aluminium as an interaction and loss of potency occurs.  
Dilute with sodium chloride 0.9% or glucose 5% (usually to 500 mL) and infuse over 1 hour.

**Patient counseling**
Tell your doctor if you occasionally get pins and needles or numbness of fingers and toes.  
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.  
It may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

**Practice points**
- IV hydration to force diuresis is not necessary, as nephrotoxicity is less common with carboplatin than with cisplatin  
- monitor complete blood count and serum creatinine before each dose of carboplatin  
- prophylactic 5HT₃ antagonists with aprepitant and dexamethasone reduce acute onset nausea and vomiting in most patients  
- use a corticosteroid with a dopamine antagonist (eg dexamethasone and metoclopramide) for delayed nausea and vomiting which occurs >1–2 days after platinum compound treatment (see Nausea and vomiting due to chemotherapy)

**Products**
CARBOPLATIN VIAL 150 MG/VIAL  15 ML VIAL (CARBOPLATIN®, CARBOPLATIN EBEWE®, CARBOSIN®, KEMOCARB®, NEOPLATIN®)  
CARBOPLATIN VIA  450 MG/VIAL  45 ML VIAL (CARBOPLATIN®, CARBOPLATIN EBEWE®, KEMOCARB®, PARAPLATIN®, NEOPLATIN®)

**CISPLATIN**
Also known as cis-DDP.

**Mode of action**
Platinum compounds are activated within the cell by displacement of chloride ions, leaving positively charged platinum molecules which react with DNA. DNA replication, transcription and cell division are inhibited, ultimately inducing apoptosis. Other mechanisms may also be involved. Platinum compounds are cell cycle nonspecific.

**Indications**
Marketed: Non-seminomatous germ cell carcinoma, Metastatic, Ovarian cancer, advanced, refractory, Bladder cancer, advanced, refractory, Squamous cell head and neck cancer, refractory.  
Accepted: Seminoma testis, Metastatic, Extra-gonadal germ cell carcinoma, adjuvant therapy or salvage therapy for relapsed, Squamous cell carcinoma of cervix, advanced, Small cell and non–small cell lung cancer, Oesophageal cancer, extraglandular germ cell carcinoma (adjuvant therapy or salvage therapy).

**Specific considerations**
Hearing impairment: further deterioration in hearing may occur.  
Treatment with neurotoxic drugs, eg paclitaxel, vincristine: additive neurotoxic effects, monitor for neuropathy.  
Allergic reaction to a platinum compound: cross-sensitivity is not absolute; if necessary, try an alternative platinum compound (with appropriate precautions).  
Treatment with other nephrotoxic drugs: additive risk of nephrotoxicity; use with caution (avoid with cisplatin).  
Exposure, eg industrial, to other platinum compounds: may produce an allergic reaction to cisplatin or carboplatin.
Renal impairment: Avoid use if creatinine clearance <30 mL/minute.

Elderly: Age-related renal impairment may require dose adjustment.

Children: Limited experience. Nausea, vomiting and ototoxicity appear to be more severe in children.

Pregnancy: Avoid use in pregnancy unless the benefits outweigh the risks; ADEC category D.

Breastfeeding: Insufficient data available; avoid use.

Adverse effects

Common: nephrotoxicity and myelosuppression; electrolyte disturbances (hypocalcaemia and hypomagnesaemia)
which may be symptomatic causing muscle irritability, cramps, clonus, tremor, carpopedal spasm and/or tetany;
hypokalaemia, hyperuricaemia; severe nausea and vomiting (acute and delayed), diarrhoea, tinnitus with or without
clinical hearing loss, sensory and motor peripheral neuropathies, myasthenia-like syndrome, seizures, anaphylactoid
reaction, local phlebitis, mild alopecia.

Infrequent: hypophosphataemia and hyponatraemia, elevation of serum transaminases and bilirubin, elevated serum
amylase, hiccups.

Rare: haemolytic anaemia, urticarial rashes, exfoliative dermatitis, vestibular toxicity, optic neuritis, papilloedema,
cerebral blindness, ECG changes and congestive cardiac failure, postural hypotension, extravasation reaction.

Myelosuppression: Less severe than with carboplatin; nadirs of neutropenia and thrombocytopenia occur
approximately 10–14 days after a dose.

Nephrotoxicity: Includes acute tubular necrosis with tubular degeneration, interstitial oedema and fibrosis, dilatation
of convoluted tubules and cast formation. Proximal and distal tubules are affected but not usually glomeruli,
although changes in glomerular filtration rate may occur. Renal toxicity is reduced with protocols including prior
hydration to force diuresis (using mannitol and frusemide).

Dosage

Consult specialist protocols. The following initial doses have been used as single agent or in combination therapy:

IV infusion, 50–100 mg/m² or
IV infusion, 15–20 mg/m² daily for 5 days.

Further courses depend on patient response and toxicity.

Administration instructions

Before starting cisplatin infusion give 1–2 L of fluid over several hours with 10% mannitol. Infuse cisplatin in 1 L of
sodium chloride 0.9% or 4% glucose in sodium chloride 0.18% over 1–2 hours. Maintain adequate hydration for at
least 24 hours after a dose.

Patient counseling

Cisplatin can cause persistent kidney damage and cause the body to lose some salts, e.g. magnesium, calcium and
potassium. You will be given extra fluids to reduce the risk of kidney damage.

Sometimes hearing loss or ringing in the ears occurs. It may also affect nerves, causing pins and needles in fingers or

Toes or difficulty in walking. Tell your doctor if you notice any of these effects.

This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your
doctor what to do if you think you may be getting one.

It may also cause you to bruise and bleed more easily. Tell your doctor if unusual
bruising or bleeding occur.

Practice points

- adequate hydration and urinary output must be maintained before, and for at least 24 hours after,
  administration
- watch for peripheral neuropathy and changes in hearing; monitor serum creatinine, electrolytes and
  complete blood count before each cycle
- oral magnesium has been given to prevent/treat hypomagnesaemia but effectiveness is uncertain
- amifostine may be used with cisplatin-containing regimens in ovarian cancer to reduce renal and neurologic
  toxicity without reducing the response rate, but its use is not routine
- prophylactic 5HT3 antagonists with aprepitant and dexamethasone reduce acute onset nausea and vomiting
  in most patients
- clinical trials show aprepitant (with a 5HT3 antagonist and dexamethasone) is effective for prevention of
  both acute and delayed nausea and vomiting associated with high dose cisplatin
- use a corticosteroid with a dopamine antagonist (e.g. dexamethasone and metoclopramide) for delayed
  nausea and vomiting which occurs >1–2 days after platinum compound treatment
- only about 50% of patients treated with cisplatin experience nausea control with any antiemetic regimen.

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OXALIPLATIN

Mode of action
Platinum compounds are activated within the cell by displacement of chloride ions, leaving positively charged platinum molecules which react with DNA. DNA replication, transcription and cell division are inhibited, ultimately inducing apoptosis. Other mechanisms may also be involved. Platinum compounds are cell cycle nonspecific.

Indications
With fluorouracil and folinic acid for:
- advanced colorectal cancer
- adjuvant treatment for stage III colon cancer after resection of primary tumour

Specific considerations
Allergic reaction to a platinum compound: cross-sensitivity is not absolute; if necessary, try an alternative platinum compound (with appropriate precautions).
Treatment with other nephrotoxic drugs: additive risk of nephrotoxicity; use with caution (avoid with cisplatin).
Exposure, eg industrial, to other platinum compounds: may produce an allergic reaction to cisplatin or carboplatin.
Renal impairment: Manufacturer contraindicates use if creatinine clearance <30 mL/minute.
Elderly: Dosage reduction due to age-related renal impairment may be required.
Children: Carboplatin has been used for brain tumour (from 6 months of age) and Wilms' tumour (2–15 years).
Adverse effects are similar to those in adults. Cisplatin has also been used to a limited extent in childhood tumours. Ototoxicity may be more severe in children. Oxaliplatin has not been used.
Pregnancy: Avoid use; ADEC category D.
Breastfeeding: Insufficient data; avoid use.

Adverse effects
Common: myelosuppression (neutropenia, thrombocytopenia, anaemia), moderate nausea and vomiting, stomatitis, mucositis, dysphagia, diarrhoea, peripheral neuropathy, dyspnoea, alopecia, myalgia, arthralgia, weakness, raised serum creatinine, hypokalaemia, metabolic acidosis, mild elevations of ALP, liver transaminases and bilirubin
Rare: ototoxicity, transient loss of vision, anaphylactic reaction, acute interstitial lung disease, pulmonary fibrosis, autoimmune haemolytic anaemia, mild-to-moderate tissue inflammation on extravasation
Peripheral neuropathy: Occurs as an acute, reversible cold-induced dysaesthesia appearing rapidly after therapy, or a persistent sensory neuropathy occurring after a total cumulative dose of 750–850 mg/m2.

Dosage
Consult specialist protocols. The following initial dose has been used with fluorouracil and folinic acid:
IV infusion, 85 mg/m2 repeated every 2 weeks. Repeated courses will depend on patient response and toxicity.

Administration instructions
Dilute with glucose 5%, usually to 500 mL, and infuse over 2–6 hours. Avoid extravasation. Flush IV lines with glucose 5%.
Incompatible with chloride or alkaline solutions
Administer before fluorouracil.
Do not prepare or administer with equipment containing aluminium as an interaction and loss of potency occurs.

Patient counseling
During the infusion and for 2 days afterwards, avoid cold foods or drinks and keep yourself warm because some side effects may occur after exposure to cold temperatures.
Tell your doctor if you develop fever, difficulty in breathing, persistent vomiting or diarrhoea or if you get pins and needles or numbness of fingers and toes.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
It may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

Practice points
- as nephrotoxicity is less common with oxaliplatin than with cisplatin, IV hydration to force diuresis is not necessary
- perform neurological examination and monitor complete blood count and serum creatinine before each dose of oxaliplatin
infusions of calcium and magnesium before and after treatment with oxaliplatin decrease incidence and intensity of acute neurotoxicity and may decrease cumulative effects

- give more slowly (over 6 hours) if patient develops laryngopharyngeal dysaesthesia
- prophylactic 5HT₃ antagonists with aprepitant and dexamethasone reduce acute onset nausea and vomiting in most patients
- use a corticosteroid with a dopamine antagonist (e.g., dexamethasone and metoclopramide) for delayed nausea and vomiting which occurs >1–2 days after platinum compound treatment (see Nausea and vomiting due to chemotherapy)

Products

OXALIPLATINE VIAL 50 MG/VIAL (ELOXATIN®)
OXALIPLATINE VIAL 100 MG/VIAL (ELOXATIN®)

08.03.07 PODOPHYLLOTOXINS

ETOPOSIDE

Also known as VP-16.

Mode of action

Etoposide is a podophyllotoxin derivative. Etoposide phosphate is a pro-drug dephosphorylated to etoposide. It acts by inhibiting topoisomerase II, they produces single strand breaks in DNA affecting the S and G2 phases of the cell cycle.

Indications


Accepted: According to specialist protocol

Contraindications

- Allergy to etoposide or polysorbate 80 (only in etoposide injection)
- Low birth weight and premature infants (etoposide injection, due to polysorbate 80)

Specific considerations

- Low plasma albumin: increases the unbound fraction of drug, increasing toxicity.
- Renal impairment: Dosage reduction may be indicated in renal impairment; monitor for increased myelosuppression; seek specialist advice.
- Hepatic impairment: Clearance may be reduced in severe impairment; monitor for increased myelosuppression.
- Pregnancy: Contraindicated; ADEC category D.
- Breastfeeding: Contraindicated; no data.

Adverse effects

Common: myelosuppression, alopecia, mild nausea and vomiting, mucositis, anorexia, constipation, abdominal pain, taste alteration, weakness, malaise.

Infrequent: hypotension (associated with infusion rate of etoposide injection), peripheral neuropathy.

Rare: anaphylaxis, heart failure, cardiac arrest, radiation recall, dermatitis, Stevens–Johnson syndrome

Myelosuppression: Affects white cells, platelets and red cells. The neutrophil nadir occurs 7–14 days after dose of etoposide (12–19 days after etoposide phosphate). Platelet nadir occurs at about 9–16 days with etoposide (10–15 days with etoposide phosphate). Recovery of the bone marrow takes about 20 days but red cells may take longer.

Dosage

Consult specialist protocols. Doses below are expressed as etoposide; each vial of 113.6 mg etoposide phosphate contains 100 mg etoposide. The following initial dose has been used:

- IV, 300–500 mg/m² divided over 3–5 days. Repeated courses depend on patient response and toxicity.
- Oral dose is generally twice the IV dose and should be taken on an empty stomach.

Administration instructions

Infuse etoposide over 1 hour to avoid hypotension and bronchospasm related to polysorbate 80.

Etoposide phosphate may be infused over 5 minutes to 3.5 hours.

Patient counseling

This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

Practice points
etoposide phosphate (a pro-drug dephosphorylated to etoposide) is safer to administer but is more expensive than etoposide

100 mg of etoposide injection contains alcohol equivalent to one-third of a standard drink; this alone is unlikely to cause adverse effects, but may have additive CNS depressant effects with other medications (eg promethazine, lorazepam)

measure complete blood count, liver function tests, serum creatinine and urea at baseline and before each cycle

Products
ETOPOSIDE CAPS 50 MG (LASTET®)
ETOPOSIDE VIAL 100 MG/VIAL  5 ML VIAL (LASTET®, ETOPOSID®, NEOPLAXOL®, FYTOSID®)

08.03.08 TAXANES

DOCETAXEL

Mode of action
Promote assembly of tubulin into stable non-functional microtubules and inhibit disassembly arresting cell cycles in late G2 and M phase.

Indications
Marketed: Breast cancer:
- node positive, adjuvant treatment (with doxorubicin and cyclophosphamide)
- locally advanced or metastatic (refractory)
Non-small cell lung cancer, locally advanced or Metastatic, Ovarian cancer, metastatic (refractory), Prostate cancer (hormone-insensitive)
Accepted: According to specialist protocol, eg for gastric cancer

Contraindications
Allergy to docetaxel or polysorbate 80
Specific considerations
Allergies, especially to bee-stings: may be at higher risk of anaphylaxis with taxanes.
Hepatic impairment: Moderate-to-severe impairment; increased incidence of adverse effects; use lower doses or avoid use.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: Contraindicated; no data.

Adverse effects
Common: myelosuppression, hypersensitivity reactions, localised rash on hands, feet, face or thorax; cumulative fluid retention (pleural effusions, ascites, peripheral oedema).
Infrequent: heart failure, arrhythmia.
Rare: desquamation of palms and soles, enterocolitis, pulmonary fibrosis.
Hypersensitivity reactions: Usually occur with the first or second cycle and within a few minutes of starting infusion; may be mild (infusion can continue) or severe (hypotension and bronchospasm requiring resuscitation); minimise by premedicating with dexamethasone. Rare cases of reversible, transient visual disturbances have occurred in association with hypersensitivity reactions.
Myelosuppression: Dose-related and limiting. Neutropenia is common, with a nadir 8–12 days after dose and recovery by about day 15–20. Anaemia is also common and may require blood transfusion. Thrombocytopenia occurs less frequently.

Dosage
Consult specialist protocols
The following initial doses have been used, repeat courses depend on patient response and toxicity.
Single agent, IV 75–100 mg/m2.
Combination therapy, IV 60–75 mg/m2.

Administration instructions
Contains solubiliser polysorbate 80; PVC administration set can be used but use diluted solution within 8 hours of preparation.
Dilute reconstituted solution to <0.74 mg/mL in either sodium chloride 0.9% or glucose 5% and infuse over 1 hour.
Avoid extravasation.

Patient counselling
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your
doctor what to do if you think you may be getting one. It may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

**Practice points**
- Premedication with dexamethasone reduces the severity and incidence of peripheral oedema and hypersensitivity reactions
- If severe cutaneous reaction or severe peripheral neuropathy occurs, reduce dose or stop docetaxel
- Emergency treatment (adrenaline, antihistamine and corticosteroid) for anaphylaxis must be readily available
- Mild adverse symptoms, such as localised rash or erythema, do not necessitate stopping treatment
- Measure complete blood count, liver function tests at baseline and before each cycle
- Monitor ECG throughout infusion if previous doses have caused cardiac abnormalities

**Products**

- **DOCETAXEL VIALS 20 MG/VIAL  0.5 ML VIAL** (TAXOTERE®, DOXETAL®)
- **DOCETAXEL VIALS 80 MG/VIAL  2 ML VIAL** (TAXOTERE®, DOXETAL®)

**PACLITAXEL**

**Mode of action**

Promote assembly of tubulin into stable non-functional microtubules and inhibit disassembly arresting cell cycles in late G2 and M phase.

**Indications**

Marketed:
- **Ovarian cancer:**
  - primary treatment (with platinum agent)
  - metastatic (refractory)
- **Breast cancer:**
  - Node positive, adjuvant treatment (with doxorubicin and cyclophosphamide)
  - unresectable or locally recurrent (with gemcitabine), after failure of therapy including an anthracycline
  - metastatic, with over-expression of HER2, first line (with trastuzumab)
  - metastatic (refractory)
- **Non-small cell lung cancer**
- **Accepted:**

**Contraindications**

- Allergy to paclitaxel or polyoxyl (PEG) 35 castor oil.

**Specific considerations**

- Treatment with fluorouracil: pretreatment with fluorouracil may inhibit cytotoxic action of paclitaxel; avoid combination.
- Treatment with neurotoxic drugs, e.g. cisplatin, vincristine: additive neurotoxic effects, monitor for neuropathy.
- Allergies, especially to bee-stings: may be at higher risk of anaphylaxis with taxanes.
- Hepatic impairment: Reduced clearance in moderate-to-severe impairment, increased incidence of adverse effects; avoid use or consider dose reduction.
- **Pregnancy:** Contraindicated; ADEC category D.
- **Breastfeeding:** Contraindicated; no data.

**Adverse effects**

- Common: elevated liver enzymes, bradycardia and ECG abnormalities, hypotension.
- Myelosuppression, mild-to-moderate dose-related nausea and vomiting, diarrhoea, stomatitis, mucositis, myalgia, arthralgia, alopecia, paraesthesia, dysaesthesia or pain including burning, mild allergic reactions (including flushing, dyspnoea, urticaria, rash which may develop 7–10 days after infusion), anaphylactic reactions, mild injection site reactions including inflammation and hyperpigmentation, nail hypo- or hyperpigmentation
- Rare: seizures, encephalopathy, chest pain, extravasation reaction.
- Myelosuppression: Dose-related and limiting. Neutropenia is common, with a nadir 8–12 days after dose and recovery by about day 15–20. Anaemia is also common and may require blood transfusion. Thrombocytopenia occurs less frequently.

**Dosage**

Consult specialist protocols. The following initial doses have been used. Further courses depend on patient response and toxicity.

Premedicate with dexamethasone 20 mg orally 12 and 6 hours before infusion, promethazine 25 mg IV and
ranitidine 50 mg IV 30 minutes before infusion.

Ovarian cancer primary treatment: 175 mg/m² given over 3 hours or 135 mg/m² given over 24 hours with cisplatin or carboplatin.

Breast cancer, non-small cell lung cancer, metastatic ovarian cancer

175 mg/m² given over 3 hours.

Administration instructions

Use non-PVC container and administration set.

Dilute to 0.3–1.2 mg/mL in either glucose 5% or sodium chloride 0.9%. Infuse IV with an in-line 0.22 micrometre (micron) filter. Avoid extravasation.

Patient counselling

This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

It may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

Practice points

- premedication with dexamethasone and H1 and H2 antagonists may reduce severity and incidence of hypersensitivity reactions
- simple analgesics may be useful to relieve arthralgias or myalgias
- both brands contain ethanol and patients may be exposed to the equivalent of 2 or more standard drinks per dose
- if severe peripheral neuropathy occurs, reduce dose to 80% of full dose
- emergency treatment (adrenaline, antihistamine and corticosteroid) for anaphylaxis must be readily available
- mild adverse symptoms, such as localised rash or erythema, do not necessitate stopping treatment
- measure complete blood count, liver function tests at baseline and before each cycle
- monitor ECG throughout infusion if previous doses have caused cardiac abnormalities

Products

PACLITAXEL VIAL 300 MG/VIAL 50 ML VIALCARBO (CELTA®, DRIFEN®, INTAXEL®, PACLITAXEL®, TAXOL®)

08.03.09 TOPISOMERASE 1 INHIBITORS

IRINOTECAN

Mode of action

Inhibit the enzyme topoisomerase 1, thereby interfering with coiling and uncoiling of DNA during replication which inhibit nucleic acid synthesis. Actions are specific for S-phase.

Indications

Metastatic colorectal cancer.

Specific considerations

Inflammatory bowel disease: increases risk of diarrhoea.

Recent or concurrent radiotherapy to abdomen or pelvis: increases risk of diarrhoea and severe neutropenia.

Asthma, cardiovascular disease, mechanical intestinal or urinary obstruction: irinotecan has cholinergic effects and may cause an aggravation of the underlying disease.

Treatment with laxatives: may increase risk of severe diarrhea with irinotecan (if patient is on opioids, consider whether laxative is necessary).

Treatment with diuretics: irinotecan may increase of dehydration; withhold diuretic during severe diarrhoea or vomiting.

Hepatic impairment: Do not use if serum bilirubin >34 micromol/L or transaminases >3 times upper limit of normal if no liver metastases present, or >5 times upper limit of normal with liver metastases.

Mildly elevated serum bilirubin (17–34 micromol/L) or Gilbert's syndrome is associated with greater risk of severe neutropenia.

Pregnancy: Avoid use; ADEC category D.

Breastfeeding: Do not use.

Adverse effects

Common: myelosuppression, moderate nausea and vomiting, anorexia, dehydration, cholinergic symptoms, e.g. diarrhoea, liver enzyme abnormalities, asthenia, alopecia, dyspnoea, cough.
Infrequent: bradycardia, syncope.
Rare: colonic ulceration, sometimes with GI bleeding, ileus (without preceding colitis), thromboembolism, extravasation reaction.
Myelosuppression: More common with elevated serum bilirubin or previous pelvic or abdominal irradiation. Neutropenia is common, with a nadir 8 days after dose and recovery by 22 days. Lymphocytopenia and anaemia are also common. Thrombocytopenia is uncommon with once a week dosing but more common when irinotecan is given in the 3-week schedule.
Diarrhoea: Acute diarrhoea within 24 hours of a dose, may be part of a cholinergergic syndrome which may also include rhinitis, sweating, salivation, abdominal cramps, lacrimation and miosis. Use SC/IV atropine 0.25–1 mg to control symptoms.
More severe, prolonged diarrhoea (which can be life-threatening) may occur, beginning >24 hours after a dose; use loperamide, e.g. 4 mg at onset of late diarrhoea, then 2 mg every 2 hours until diarrhoea-free for 12 hours, or 4 mg every 4 hours during the night. Consider fluid and electrolyte replacement and withholding irinotecan treatment; reduce any further doses of irinotecan. Median time to onset of late diarrhoea in trials was 11 days for weekly schedule and 5 days for the 3-week schedule.

**Dosage**
Consult specialist protocols
The following initial doses have been used; further doses depend on patient response and toxicity.
IV infusion, 125 mg/m² each week initially or 350 mg/m² every 3 weeks
Elderly: Use a lower starting dose for the 3-week schedule as more severe late onset diarrhoea in the elderly has been observed with this regimen.

**Administration instructions**
IV infusion in 250–500 mL glucose 5% over 90 minutes. Avoid extravasation.

**Patient counseling**
Tell your doctor immediately if diarrhoea develops, as it can be serious if not treated quickly.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

**Practice points**
- in first line therapy of advanced colorectal cancer irinotecan with fluorouracil and folinic acid increases survival by 2–3 months (but with increased toxicity) compared to irinotecan monotherapy or fluorouracil with folinic acid
- increased toxicity and death have been reported with the fluorouracil 5-day bolus regimen with irinotecan; use alternative fluorouracil administration regimen
- obtain complete blood count and liver function tests before each dose of irinotecan
- note bowel patterns before irinotecan therapy; monitor and treat immediately with loperamide if bowel frequency increases after irinotecan administration.

**Products**
IRINOTECAN VIAL 40 MG/VIAL (AS HCL) 2 ML VIAL (CAMPTO®)
IRINOTECAN VIAL 100 MG/VIAL (AS HCL) 5 ML VIAL (CAMPTO®, IRINOTECAN®)

**TOPOTECAN**

**Mode of action**
Inhibit the enzyme topoisomerase 1, thereby interfering with coiling and uncoiling of DNA during replication which inhibits nucleic acid synthesis. Actions are specific for S-phase.

**Indications**
Marketed: Small cell lung cancer after failure of first line chemotherapy, Ovarian cancer after failure of platinum-based chemotherapy.
Accepted: Acute myeloid leukaemia, refractory or relapsed, Cervical cancer, recurrent or metastatic.

**Contraindications**
Allergic reaction to topotecan.

**Specific considerations**
Renal impairment: If creatinine clearance 20–40 mL/minute, reduce dose; do not use in moderate-to-severe impairment.
Pregnancy: Avoid use; ADEC category D.
Breastfeeding: Do not use.

**Adverse effects**

Common: moderate nausea and vomiting, diarrhoea, myelosuppression, fatigue, weakness, alopecia, anorexia, headache, dizziness, dyspnoea, coughing, epistaxis, pharyngitis, rhinitis.

Infrequent: neuropathy, peripheral neuropathy, constipation, stomatitis, rash, hyperbilirubinaemia, elevated transaminases.

Rare: allergic reactions, mild extravasation reaction.

Myelosuppression: Neutropenia is common, with a nadir 8 days after dose and recovery by 22 days.

**Dosage**

Consult specialist protocols.

The following initial doses have been used. Further courses depend on patient response and toxicity.

*IV*, 1.5 mg/m$^2$ daily on days 1–5 of 21-day course.

Renal impairment: *Creatinine clearance 20–40 mL/minute*, IV, 0.75 mg/m$^2$ daily.

**Administration instructions**

IV infusion in 100 mL of sodium chloride 0.9% or glucose 5% over 30 minutes. Avoid extravasation.

**Patient counselling**

This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.

This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.

**Practice points**

- obtain complete blood count, serum creatinine and liver function before each course

**Products**

TOPOTECAN VIAL 4 MG/VIAL (AS HCL) (HYCAMTIN®)

**08.03.10 VINCA ALKALOD**

**VINBLASTINE**

**Mode of action**

Block mitosis by arresting cells in metaphase. Cell cycle specific for M phase.

**Indications**

Marketed: Hodgkin's disease, Non-Hodgkin's lymphoma, Advanced mycosis fungoides, Advanced carcinoma of the testis, Kaposi's sarcoma, Letterer-Siwe disease (histiocytosis X), Choriocarcinoma (unresponsive to other treatment), Breast cancer (unresponsive to surgery and hormonal treatment).

Accepted: Refractory idiopathic immune thrombocytopenic purpura, Bladder cancer.

**Contraindications**

Intrathecal injection (fatal).

**Specific considerations**

Treatment with ototoxic drugs: potential for additive ototoxicity; avoid combination or monitor for ototoxicity.

Elderly: Cachexia or skin ulcers: increased risk of neutropenia; reduce dose by half.

Hepatic impairment: Dose reduction may be required.

Pregnancy: Contraindicated; ADEC category D.

Breastfeeding: No data.

**Adverse effects**

Common: mild nausea and vomiting, hair loss, constipation, peripheral and autonomic neuropathy, abdominal pain.

Infrequent: GI bleeding, paralytic ileus.

Rare: acute shortness of breath and bronchospasm, (may be progressive); nerve damage may result in peripheral neuritis, loss of deep tendon reflexes, headache, convulsions, psychosis, ataxia, parotid gland pain, mental depression; SIADH may occur at higher than recommended doses; MI. temporary or permanent vestibular and auditory nerve damage (deafness, balance difficulties or nystagmus)

Myelosuppression: Myelosuppression affecting white cells is common; platelets and red cells are less frequently affected. The white cell nadir occurs at about 5 days after a dose, with recovery by 7–14 days.

Extravasation: Extravasation results in cellulitis, phlebitis and necrosis. Apply warm compresses to extravasation site to minimise crystallisation of vinca alkaloid in tissues; SC hyaluronidase may be used; consult specialist centre.

**Dosage**
Consult specialist protocols. The following initial dose has been used. Repeat dosing depends on response and toxicity.

**Combination therapy, IV 3–6 mg/m² every 7 days.**

**Administration instructions**
Give IV over 1 minute or by short infusion into side arm of a fast running sodium chloride 0.9% infusion. Avoid extravasation.

**Patient counselling**
Tell your doctor or nurse immediately if you feel any pain, stinging or burning during the injection or infusion. This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one. Tell your doctor if you become constipated, have unusual bruising or bleeding or if you notice numbness or tingling.

**Practice points**
- obtain complete blood count at baseline and before subsequent doses
- stop treatment if pulmonary symptoms (e.g. bronchospasm, dyspnoea) develop
- do not inject into an extremity with impaired circulation (e.g. due to invading cancer, phlebitis, varicosity, local compression); thrombosis may occur
- to minimise risk of inadvertent intrathecal administration some centres put doses of vinca alkaloid into 50–100 mL of sodium chloride 0.9%

**Products**
VINBLASTINE AMPS 10 MG/AMP (AS SULFATE) (NOT REGISTERED)

**VINCRISTINE**

**Mode of action**
Block mitosis by arresting cells in metaphase. Cell cycle specific for M phase.

**Indications**
Used for a wide variety of solid tumours and haematologic malignancies.

**Contraindications**
Demyelinating Charcot–Marie–Tooth syndrome.
Current radiotherapy to the liver.
Intrathecal injection (fatal).

**Specific considerations**
Treatment with ototoxic drugs: potential for additive ototoxicity; avoid combination or monitor for ototoxicity.
Treatment with neurotoxic agents (e.g. colaspase): potential for additive neurotoxicity; avoid combinations. Give vincristine 12–24 hours before colaspase if combination indicated.
Elderly: Increased susceptibility to neurotoxicity.
Hepatic impairment: Dose reduction may be required.
Pregnancy: Contraindicated; ADEC category D.
Breastfeeding: No data.

**Adverse effects**
Common: jaw pain (after first and second doses only), mild nausea and vomiting, hair loss, constipation, peripheral and autonomic neuropathy, abdominal pain.
Infrequent: progressive peripheral nerve and autonomic nerve dysfunction (urinary retention, orthostatic hypotension) with continued therapy, paralytic ileus.
Rare: acute shortness of breath and bronchospasm, which may be progressive; SIADH at higher than recommended doses, anaphylaxis. temporary or permanent vestibular and auditory nerve damage (deafness, balance difficulties or nystagmus).
Myelosuppression: Myelosuppression affecting white cells is common except for vincristine; platelets and red cells are less frequently affected. The white cell nadir occurs at about 5 days after a dose, with recovery by 7–14 days.
Extravasation: Extravasation results in cellulitis, phlebitis and necrosis. Apply warm compresses to extravasation site to minimise crystallisation of vinca alkaloid in tissues; SC hyaluronidase may be used; consult specialist centre.

**Dosage**
Consult specialist protocols.

**Administration instructions**
Vincristine is irritant and must not be given IM, SC or intrathecally. Intrathecal administration of vincristine has resulted in death.
To reduce risk of accidental intrathecal administration give vincristine in 50 mL bag of sodium chloride 0.9% as IV
bolus over 5–10 minutes; reduce fluid volume in bag and use slower rate of administration for children.
Alternatively, give IV over 1 minute or by short infusion into side arm of a fast running sodium chloride 0.9% infusion. Avoid extravasation

**Patient counseling**
Tell your doctor or nurse immediately if you feel any pain, stinging or burning during the injection or infusion. This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
Tell your doctor if you become constipated, have unusual bruising or bleeding or if you notice numbness or tingling.

**Practice points**
- give prophylactic therapy for constipation (eg docusate with senna)
- monitor for asymptomatic depression of Achilles reflex (commonly precedes neuropathy)
- in adults minimise neurotoxicity by limiting a single dose to 2 mg and cumulative doses to 20 mg; higher cumulative doses may be used in selected patients over periods of 1–2 years
- children tolerate vincristine better than adults
- obtain complete blood count at baseline and before subsequent doses
- stop treatment if pulmonary symptoms (eg bronchospasm, dyspnoea) develop
- do not inject into an extremity with impaired circulation (eg due to invading cancer, phlebitis, varicosity, local compression); thrombosis may occur
- to minimise risk of inadvertent intrathecal administration some centres put doses of vinca alkaloid into 50–100 mL of sodium chloride 0.9%

**Products**
- VINCRISTIN VIAL 1 MG/VIAL (AS SULFATE) 1 ML VIAL (PHARMACRISTINE®, VINCRISTINE SULPH.®, V.C.S® , VINCRISTINE®)
- VINCRISTIN VIAL 2 MG/VIAL (AS SULFATE) 2 ML VIAL (VINCRISTINE SULPH.®, VINCRISTINE®)
- VINORELBINE

**Mode of action**
Block mitosis by arresting cells in metaphase. Cell cycle specific for M phase

**Indications**
Advanced breast cancer where other therapy has failed
Advanced non–small cell lung cancer

**Contraindications**
Intrathecal injection (fatal).

**Specific considerations**
- Hepatic impairment: Dose reduction may be required.
- Pregnancy: Contraindicated; ADEC category D.
- Breastfeeding: No data.

**Adverse effects**
Common: mild nausea and vomiting, hair loss, constipation, peripheral and autonomic neuropathy, abdominal pain.
Infrequent: chest pain, paralytic ileus.
Rare: acute shortness of breath and bronchospasm which may progress, SIADH. temporary or permanent vestibular and auditory nerve damage (deafness, balance difficulties or nystagmus)
Myelosuppression: Myelosuppression affecting white cells is common except for vincristine; platelets and red cells are less frequently affected. The white cell nadir occurs at about 5 days after a dose, with recovery by 7–14 days.
Extravasation: Extravasation results in cellulitis, phlebitis and necrosis. Apply warm compresses to extravasation site to minimise crystallisation of vinca alkaloid in tissues; SC hyaluronidase may be used; consult specialist centre.

**Dosage**
Consult specialist protocols. The following initial doses have been used. Repeat dosing depends on response and toxicity.
- Single agent, IV 25–30 mg/m² every 7 days.
- Combination therapy, IV 25–30 mg/m2 on days 1 and 8, repeated every 21 days.
- Repeat dosing depends on patient response and toxicity.

**Administration instructions**
Give IV over 6–10 minutes or by short infusion into side arm of a fast running sodium chloride 0.9% infusion. Avoid extravasation
Patient counseling
Tell your doctor or nurse immediately if you feel any pain, stinging or burning during the injection or infusion. This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
Tell your doctor if you become constipated, have unusual bruising or bleeding or if you notice numbness or tingling.

Practice points
- obtain plasma bilirubin concentration before each dose
- give prophylactic therapy for constipation (eg docusate with senna)
- monitor for asymptomatic depression of Achilles reflex (commonly precedes neuropathy); treatment may be continued if benefits outweigh risks; seek specialist advice
- obtain complete blood count at baseline and before subsequent doses
- stop treatment if pulmonary symptoms (eg bronchospasm, dyspnoea) develop
- do not inject into an extremity with impaired circulation (eg due to invading cancer, phlebitis, varicosity, local compression); thrombosis may occur
- to minimise risk of inadvertent intrathecal administration some centres put doses of vinca alkaloid into 50–100 mL of sodium chloride 0.9%

Products
VINORELBINE VIAL 50 MG/VIAL 5 ML VIAL (NAVELBINE®)

08.03.11 OTHER ANTI NEOPLASTIC DRUGS

ALEMTUZUMAB

Mode of action
Alemtuzumab is a monoclonal antibody which causes lysis of B lymphocyte.

Indications
Treatment of B-cell chronic lymphocytic leukaemia resistant to conventional chemotherapy.

Contraindications
Alemtuzumab is contra-indicated for patients with active systemic infection, or underlying immunodeficiency.

Specific considerations
Pregnancy: Avoid use in pregnancy; manufacturer advises effective contraception during and for the 6 months after administration to men or women..

Breastfeeding: manufacturer advises avoid breast-feeding for at least 4 weeks after administration.

Adverse effects
Common: neutropenia, thrombocytopenia, anaemia, or pancytopenia, severe and prolonged myelosuppression, infusion-related reactions due to an acute cytokine release syndrome, fatigue, arthralgia, myalgia, back pain, chest pain, hypertension, and tachycardia. infusion-related reaction usually includes mild to moderate rigors, fever, nausea and vomiting, hypotension, rash, urticaria, pruritus, shortness of breath, headache, and diarrhoea. More serious reactions have occurred, including bronchospasm, syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, myocardial infarction, and cardiac arrest.

Infrequent: Auto-immune thrombocytopenia and haemolytic anaemia.

Dosage
The initial dose is 3 mg daily, given as an intravenous infusion over 2 hours (it may be increased up to 8 hours in some patients. When this dose is tolerated, the dose is gradually increased until 10 mg daily can be tolerated. The maintenance dose of 30 mg can then be started; this dose escalation usually takes 3 to 7 days. A maximum maintenance dose of 30 mg given three times per week on alternate days can then be used for up to 12 weeks. The dose should be modified according to haematological toxicity.

Administration instructions
Alemtuzumab should be filtered via a 5 micron filter prior to dilution in 100 mL sodium chloride 0.9% or glucose 5%.

Practice points
- single doses greater than 30 mg, or cumulative weekly doses greater than 90 mg should not be used, because of the increased incidence of pancytopenia
- complete blood and platelet counts should be measured weekly during alemtuzumab therapy, and more frequently if anaemia, neutropenia, or thrombocytopenia occur; treatment should be discontinued if severe myelosuppression or evidence of haematological toxicity are seen.
these reactions are most common at the start of therapy: the dose must be increased gradually when beginning treatment, or if it is interrupted for 7 days or more. Pre-medication with an oral or intravenous corticosteroid, oral antihistamine, and paracetamol should also be used, particularly before the first dose, and with dose increases. If acute infusion reactions persist, the infusion time may be extended to 8 hours from the time of reconstitution.

Products
ALEMTUZUMAB VIAL 30 MG/VIAL (MABCAMPATH®)

DACARBAZINE
Also known as DIC or DTIC
Mode of action
Interfere with cellular replication by forming cross-linkages between DNA strands.
Indications
Marketed: Malignant melanoma, Metastatic, Ewing's sarcoma, rhabdomyosarcoma, Neuroblastoma.
Accepted: Hodgkin's disease.
Contraindications
Allergic reaction to dacarbazine or temozolomide
Specific considerations
Treatment with fotemustine: sequential use with dacarbazine has caused acute respiratory distress syndrome; avoid combination.
Renal impairment: Reduce dose in mild-to-moderate impairment; avoid in severe disease.
Hepatic impairment: Reduce dose in mild-to-moderate impairment; avoid in severe disease.
Pregnancy: Can produce spontaneous abortion, fetal loss and birth defects. ADEC category D.
Breastfeeding: Insufficient data; do not use.
Adverse effects
Common: myelosuppression, nausea and vomiting, diarrhoea, flu-like syndrome (fever, myalgia, malaise), transient increases in hepatic transaminases and ALP, facial flushing, pain along injected vein.
Infrequent: agranulocytosis causing death, blurred vision, seizures, confusion, headache, alopecia, erythematous and maculopapular rash, photosensitivity.
Rare: intractable nausea and vomiting, hepatic vein thrombosis and hepatocellular necrosis, tissue damage due to extravasation.
Infertility: Alkylating agents have more adverse effects on reproductive function than other classes of cytotoxic agents. Primary ovarian failure has been reported with melphalan and early menopause with cyclophosphamide. Alkylating agents used in childhood may reduce fertility, particularly in males.
Secondary malignancies: All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.
Dosage
Consult specialist protocols. The following initial doses have been used in single or combination therapy. Further courses depend on patient response and toxicity.
Melanoma: IV infusion, 250 mg/m² daily on days 1–5 of each 21-day cycle, or 800 mg/m² on day 1 of each 21-day cycle.
Hodgkin's disease: Combination treatment with other agents, adult, IV infusion 150 mg/m² each day on days 1–5 of each 28-day cycle, or 375 mg/m² on day 1 and day 15 of each 28-day cycle.
Administration instructions
IV infusion over 30–60 minutes. Avoid extravasation
Patient counselling
For the first few days after your treatment avoid direct sun exposure, use a sunscreen with a high SPF and wear protective clothing when outdoors.
This medicine may increase your chances of getting an infection. Avoid people with infections and discuss with your doctor what to do if you think you may be getting one.
This medicine may also cause you to bruise and bleed more easily. Tell your doctor if unusual bruising or bleeding occur.
Practice points
- obtain complete blood count, liver function and serum creatinine before each cycle
• nauseas and vomiting become less severe on repeated daily dosing.

Products
DACARBAZINE VIAL 100 MG/VIAL (NOT REGISTERED)
DACARBAZINE VIAL 200 MG/VIAL (NOT REGISTERED)

THALIDOMIDE

Mode of action
The mode of action is not fully understood. It inhibits production and reduces half-life of tumour necrosis factor, modulating immune and inflammatory responses to infection and has the ability to promote T cell responses without inhibiting normal immunity.
It also has anti-angiogenesis effects.

Indications
Marketed: Erythema nodosum leprosum, Multiple myeloma after failure of standard treatment.
Accepted: Inflammatory and/or skin disorders (e.g. Behcet's syndrome, chronic cutaneous lupus erythematosus, prurigo nodularis, Crohn's disease), HIV (e.g. wasting syndrome, aphthous stomatitis, diarrhoea, Kaposi's sarcoma), Neoplastic diseases, e.g. glioblastoma multiforme, Graft-versus-host disease.

Contraindications
Females who are or may become pregnant

Specific considerations
Treatment with neurotoxic agents (e.g. paclitaxel, vincristine, cisplatin): additive toxicity; avoid combination.
Elderly: May be at greater risk of peripheral neuropathy.
Children: Limited experience with use in children.
Pregnancy: Contraindicated, Teratogenic; ADEC category X. Women should use effective contraception for 1 month before starting treatment, during treatment and for 1 month after stopping thalidomide.
Males (including those who have had a vasectomy) should use a condom for sexual intercourse with a fertile female for 1 month before starting treatment, during treatment and for 1 month after stopping thalidomide.
Breastfeeding: No information; avoid use.
Adverse effects
Common: rash, sedation, somnolence, fatigue, constipation, peripheral neuropathy (e.g. painful paraesthesia of the hands and feet, muscle weakness and cramps), may be irreversible, generally occur after months of use but may occur with short term use: headache, dizziness, vertigo, tremor, agitation, nervousness, depression, insomnia, itch, peripheral oedema, diarrhoea, nausea, vomiting, weight gain, asthenia, haematuria, leucopenia.
Rare: Stevens–Johnson syndrome, pancytopenia, deep vein thrombosis, bradycardia.

Dosage
Dosage and optimal duration of treatment have not been clearly defined. Dose may be divided.
Erythema nodosum leprosum: Initially, 100–300 mg daily, up to maximum 400 mg daily. If <50 kg bodyweight start at lower end of dosage range. Reduce dose by 50 mg every 2–4 weeks when signs and symptoms subside.
Graft-versus-host disease: 800–1600 mg daily.
Multiple myeloma, glioblastoma: Consult specialist protocols.
Recurent aphthous stomatitis: 100–300 mg daily up to 400–600 mg daily.
Wasting syndrome: 100–400 mg daily.
Chronic cutaneous lupus erythematosus: 50–400 mg daily.

Patient counseling
Take at least 1 hour after food and preferably at night to avoid feeling sleepy during the day.
Sleepiness and dizziness usually occur only in the first 2 weeks of treatment; avoid driving or using machinery if you are affected.
Tell your doctor immediately if you have any numbness, tingling or pain in your hands or feet.

Practice points
• obtain a negative pregnancy test before starting thalidomide and each month during treatment and ensure effective contraception before, during and after treatment.

Products
THALIDOMIDE TABS 50 MG (NOT REGISTERED)
THALIDOMIDE TABS 100 MG (NOT REGISTERED)
TRETINOIN
Oral retinoid

Mode of action
Induces differentiation and inhibits cell proliferation in haemopoietic cell lines.

Indications
Promyelocytic leukaemia, induction and maintenance treatment in untreated or relapsed patients.

Contraindications
Pregnancy.

Specific considerations
Treatment with tetracyclines: increases risk of increased intracranial pressure; avoid combinations (contraindicated by manufacturer).
Children: Increased incidence of headache and pseudotumour cerebri.
Pregnancy: Contraindicated. Teratogenic; ADEC category X. Women should use effective contraception for 1 month before starting treatment, during treatment and for 1 month after stopping treatment.
Breastfeeding: Do not breastfeed.

Adverse effects
Common: retinoic acid syndrome, fever, dry skin and mucous membranes, rash, itch, peripheral oedema, elevated cholesterol and triglycerides (incidence 60%), cardiac events including arrhythmia (incidence 3%), stomatitis, nausea, vomiting, abdominal pain, diarrhoea, constipation, pancreatitis, malaise, oedema, flushing, thrombosis, dizziness, confusion, intracranial hypertension and pseudotumour cerebri (mainly in children), anxiety, depression, paraesthesias, insomnia, vision and hearing disorders, headache, increased sweating.

Retinoic acid syndrome: Up to 25% incidence, often associated with rapid increase in white cell count, characterised by fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, episodic hypotension and acute renal failure. Clinical trials are evaluating the effectiveness of prophylactic corticosteroids.

Dosage
Consult specialist protocols. The following induction dose has been used:
45 mg/m² daily in 2 divided doses.
Further courses depend on patient response and toxicity.

Patient counseling
This medicine is absorbed best if taken with food.
During treatment contact lenses may become uncomfortable and you may need to wear glasses instead.
Avoid excessive sun exposure, wear protective clothing and use a sunscreen.

Practice points
- monitor complete blood count, cholesterol and triglycerides, coagulation profile, liver and renal function before starting treatment and frequently during the course of treatment
- confirm a negative pregnancy test in the 2 weeks before treatment, then start on the second or third day of the next menstrual cycle; perform pregnancy tests each month during therapy.

Products
TRETINOIN CAPS 10 MG (VESANOID®)

08.04. HORMONAL ANTINEOPLASTIC DRUGS

08.04.01 ANTIANDROGENS

BICALUTAMIDE

Mode of action
Competitive blockade at androgen receptors; inhibit androgen activity.

Indications
Marketed: Locally advanced prostate cancer (150 mg), Advanced prostate cancer with GnRH analogue (50 mg).
Accepted: Prevention of GnRH analogue-associated initial tumour flare, seek specialist advice.

Specific considerations
Hepatic impairment: Monitor liver enzymes; consider dose reduction in severe impairment.

Adverse effects
50 mg dose generally well tolerated with few withdrawals due to adverse effects in clinical trials.
Common: dizziness, dyspnoea, diarrhoea, dry skin, weakness, dry mouth, flatulence; breast pain, gynaecomastia (with 150 mg dose), nausea, vomiting, increased transaminase concentrations, impotence, reduced libido, hot flushed,
body hair loss, sweating, gynaecomastia, breast pain, itch, weight changes, headache, mood changes, insomnia, lethargy
Infrequent: jaundice, hepatitis.
Rare: anaemia, thrombocytopenia, cardiovascular disorders (angina, heart failure, arrhythmias, ECG changes), interstitial pneumonitis, pulmonary fibrosis, hepatic failure (sometimes fatal with cyproterone)

**Dosage**
Locally advanced prostate cancer: 150 mg once daily for at least 2 years or until disease progression.
Advanced prostate cancer: 50 mg once daily started with GnRH analogue.

**Patient counseling**
See doctor immediately if you have difficulty breathing, yellowing of the skin or eyes, dark urine or itch.

**Practice points**
- monitor liver function tests at baseline, then every 3 months
- when used with GnRH analogue to suppress tumour flare, start antiandrogens 2 weeks before GnRH analogue and continue for 2–4 weeks
- if there is a risk of spinal cord compression or ureteric obstruction it is important to start antiandrogens first; consider orchidectomy for rapid castrate levels of androgen
- monitor liver function tests at baseline, then at regular intervals,
- transaminases usually return to normal with continued treatment; stop antiandrogen treatment if transaminase concentrations exceed 3 times upper limit of normal range
- withdrawal of nonsteroidal antiandrogen should precede the use of more toxic treatments for hormone-refractory prostate cancer as paradoxical disease regression may occur.

**Products**
BICALUTAMIDE TABS 50 MG (CASODEX®)

**FLUTAMIDE**

**Mode of action**
Competitive blockade at androgen receptors; inhibit androgen activity.

**Indications**
Advanced prostate cancer with gonadotrophin-releasing hormone (GnRH) analogue.
Prevention of GnRH analogue-associated initial tumour flare
Locally advanced prostate cancer (bicalutamide 150 mg).

**Contraindications**
Severe hepatic impairment, except if due to metastases

**Specific considerations**
G6PD deficiency, haemoglobin M disease, smokers: monitor methaemoglobin concentration; flutamide metabolite may cause methaemoglobinemia, haemolytic anaemia.

**Adverse effects**
Common: diarrhea, nausea, vomiting, increased transaminase concentrations, impotence, reduced libido, hot flushes, body hair loss, sweating, gynaecomastia, breast pain, itch, weight changes, headache, mood changes, insomnia, lethargy.
Infrequent: peripheral oedema, dizziness, blurred vision, thirst, photosensitivity, amber or yellow–green urine, galactorrhoea, jaundice, hepatitis.
Rare: hepatic failure, anaemia, haemolytic anaemia, leucopenia, sulphhaemoglobinemia, methaemoglobinemia, systemic lupus erythematosus-like syndrome, interstitial pneumonitis, pulmonary fibrosis.

**Dosage**
250 mg 2–3 times daily.

**Patient counseling**
See your doctor immediately if you notice yellowing of the skin or eyes, dark urine, itch. Avoid excessive exposure to the sun, wear protective clothing and use a sunscreen.

**Practice points**
- when used with GnRH analogue to suppress tumour flare, start antiandrogens 2 weeks before GnRH analogue and continue for 2–4 weeks
- if there is a risk of spinal cord compression or ureteric obstruction it is important to start antiandrogens first; consider orchidectomy for rapid castrate levels of androgen
- monitor liver function tests at baseline, then at regular intervals
- transaminases usually return to normal with continued treatment; stop antiandrogen treatment if transaminase concentrations exceed 3 times upper limit of normal range
- withdrawal of nonsteroidal antiandrogen should precede the use of more toxic treatments for hormone-refractory prostate cancer as paradoxical disease regression may occur.

**Products**

FLUTAMIDE TABS 250 MG (CURESTAT®, EULEXIN®, FLUTAN®)

### 08.04.02 ANTIOSTROGENS

**TAMOXIFEN**

**Mode of action**
Compete with oestrogen for receptor sites in breast tissue (anti-oestrogenic effect) resulting in inhibition of tumour growth. Also have oestrogen agonist activity on endometrium, bone and lipids. Suppression of other growth factors and cytokines may occur.

**Indications**
- Breast cancer, adjuvant therapy to reduce the risk of recurrence of oestrogen receptor-positive tumours, irrespective of menopausal status, after surgical resection of primary tumour
- Treatment of women with metastatic breast cancer
- Adjuvant therapy with cancer chemotherapy to reduce the risk of recurrence and death in women with node-positive or node-negative breast cancer

**Contraindications**
- Prophylaxis of breast cancer in women with history of thromboembolic disease.
- Serious allergic reaction to the anti-oestrogen.

**Specific considerations**
- Pre-existing endometrial hyperplasia: increased risk of endometrial cancer.
- History of thromboembolic disease: increased risk of thrombosis if taking cytotoxic agents concurrently.
- Pregnancy: Avoid use; possible effects on fetal development; use contraception during treatment and for 2 months after stopping; ADEC category B3.
- Breastfeeding: no information available; avoid use.

**Adverse effects**
- Common: hot flushes, mild nausea, fluid retention, headache, vaginal dryness and discharge.
- Infrequent: musculoskeletal pain, increased bone and tumour pain, hypercalcaemia, vaginal bleeding, endometrial hyperplasia, rash, hair thinning, thrombophlebitis, dizziness, deep vein thrombosis, pulmonary embolism.
- Rare: endometrial cancer, interstitial pneumonitis, allergy, angioedema, Stevens–Johnson syndrome, bullous pemphigoid, uterine fibroids, polyps, leucopenia, thrombocytopenia, corneal changes, retinopathy, decreased visual acuity (prolonged treatment).
- Flare reactions: Assess patient for clinical or biochemical signs of hypercalcaemia after starting treatment. Flare reactions, with increased bone pain, are common in patients with extensive bone metastases. Treat symptomatically, consider starting a bisphosphonate, and continue treatment.

**Dosage**
- 20–40 mg daily.

**Patient counseling**
Tell your doctor if you develop abnormal vaginal bleeding, vaginal discharge or pain or pressure in the pelvic region while you are taking tamoxifen or after you have stopped taking it.

**Practice points**
- women treated with adjuvant tamoxifen for 1–5 years have a reduction of 13–47% in the incidence of contralateral breast cancer
- available evidence indicates optimal duration of tamoxifen therapy is 5 years
- prophylactic use of tamoxifen to reduce the incidence of breast cancer in women at high risk, e.g. family history of breast cancers, is currently being evaluated
- there is a small increased risk of endometrial cancer, pulmonary embolism, deep venous thrombosis and stroke with tamoxifen and a careful assessment of risk-benefit should be made before starting prophylactic therapy in healthy women
- when used as an adjuvant, anti-oestrogens are given sequentially at completion of chemotherapy; combined cytotoxic–anti-oestrogen treatment increases disease-free survival but benefit for 'cure' or overall survival has not been shown
• treatment of metastatic breast cancer is generally continued until disease progression occurs; the median duration of response is 8–14 months
• in metastatic disease measure plasma calcium at baseline, then each week for 2 weeks, then each month
• soft tissue disease (nodes, skin) and bone respond better to anti-oestrogens than visceral sites; cytotoxic therapy is preferred if disease is visceral (e.g. interstitial lung) and more rapid control is required
• hormone receptor concentrations aid treatment selection.

Products
TAMOXIFEN TABS 20 MG (AS CITRATE) (MEDOTAMIFEN®, NOLVADEX®, NOVOFEN®, TAMOCIT®, TAMOFEN®, TAMOXIFEN EBEWE®)

08.04.03 AROMATASE INHIBITORS

08.04.03 01. NONSTEROIDAL AROMATASE INHIBITORS

ANASTROZOLE
Mode of action
Aromatase enzymes (present in fat, liver, muscle and normal and neoplastic breast tissue in postmenopausal women) convert circulating androstenedione and testosterone into oestriol and oestradiol. Aromatase inhibitors reduce tissue oestrogen concentration.

Indications
Adjuvant treatment of early breast cancer in postmenopausal women with oestrogen/progestogen receptor-positive disease
Hormone-dependent advanced breast cancer in postmenopausal women.
Advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy
Breast cancer

Specific considerations
Pregnancy: Avoid use; ADEC category C.
Breastfeeding: No data.

Adverse effects
Common: hot flushes, weakness, headache, nausea, diarrhoea, vaginal dryness, musculoskeletal pain, fractures, hair thinning, rash
Infrequent: vomiting, dyspepsia, somnolence, vaginal bleeding
Rare: lymphocytopenia, increase in transaminases, angioedema, anaphylaxis, erythema multiforme, Stevens–Johnson syndrome

Dosage
1 mg daily.

Practice points
• monitor bone mineral density before and during treatment
• efficacy has not yet been demonstrated in patients with oestrogen receptor-negative tumours
• use in premenopausal women has not been established
• clinical trials are being conducted to determine optimal sequencing and clinical effectiveness of aromatase inhibitors.

Products
ANASTROZOLE TABS 1 MG (ARIMIDEX®)

LETRAZOLE
Mode of action, Specific considerations, Adverse effects, and Practice points
Same as anastrozole

Indications
Advanced breast cancer in postmenopausal women; first line or after disease progression following anti-oestrogen therapy
Extended adjuvant treatment for early breast cancer in postmenopausal women after standard adjuvant tamoxifen treatment

Dosage
2.5 mg daily.
**Practice points**

- Initial clinical trial results in early breast cancer in postmenopausal women show that letrozole improves disease-free survival (not overall survival) compared to placebo after 5 years of tamoxifen treatment.
- Efficacy has not been demonstrated in patients with oestrogen receptor-negative tumours.
- Use in premenopausal women has not been established.
- Clinical trials are being conducted to determine optimal sequencing and clinical effectiveness of aromatase inhibitors.

**Products**

- LETROZOLE TABS 2.5 GM (FEMARA®)

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**08.04.03 02. STEROIDAL AROMATASE INHIBITORS**

**EXEMESTANE**

**Mode of action**

Aromatase enzymes (present in fat, liver, muscle and normal and neoplastic breast tissue in postmenopausal women) convert circulating androstenedione and testosterone into oestriol and oestradiol. Aromatase inhibitors reduce tissue oestrogen concentration.

**Indications**

Advanced breast cancer in postmenopausal women with disease progression following anti-oestrogen therapy.

**Specific considerations**

- Pregnancy: Avoid use; ADEC category C.
- Breastfeeding: No data.

**Adverse effects**

Common: headache, nausea and vomiting, vaginal bleeding or spotting, leucorrhoea.

Infrequent: dyspnoea, thrombophlebitis (superficial and deep), leg cramp, flatulence, peripheral oedema, fatigue, hot flushes, hair thinning, rash, dyspepsia, weakness, musculoskeletal pain, constipation, somnolence.

Rare: lymphocytopenia, increase in transaminases.

**Dosage**

25 mg daily.

**Patient counseling**

This medicine is absorbed best if taken after food.

**Practice points**

- Initial clinical trial results in early breast cancer in postmenopausal women show that exemestane given after 2–3 years of tamoxifen treatment (total 5 years treatment) improves disease-free survival (not overall survival) compared to 5 years of tamoxifen treatment.
- Efficacy has not yet been demonstrated in patients with oestrogen receptor-negative tumours.
- Use in premenopausal women has not been established.
- Clinical trials are being conducted to determine optimal sequencing and clinical effectiveness of aromatase inhibitors.

**Products**

- EXEMESTANE TABS 25 MG (AROMACIN®)

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**MEGESTROL**

**Mode of action**

As for progestogens in general.

**Indications**

- Palliative treatment of various cancers.
- Anorexia and cachexia in patients with cancer or AIDS.

**Specific considerations**

As for progestogens in general.

**Adverse effects**

As for progestogens in general.

**Dosage**

Endometrial carcinoma: 40 to 320 mg daily in divided doses.
Breast cancer: 40 mg four times daily or 160 mg once daily.
Anorexia and cachexia in patients with cancer or AIDS: 800 mg daily, as oral suspension, for one month, followed by a maintenance dose of 400 to 800 mg daily.

Practice points
- Megestrol has glucocorticoid-like properties which can result in adrenocortical insufficiency severe enough to require replacement therapy with hydrocortisone.
- Megestrol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals.

Products
MEGESTROL SUSPENSION 40 MG/ML (AS ACETATE) (MEGACE®)

08.05 DRUGS USED WITH ANTINEOPLASTICS

08.05.01 COLONY STIMULATING FACTOR

FILGRASTIM
Mode of action
Ancestim is a recombinant stem cell factor which stimulates the growth of primitive progenitors which then can mature into any blood cell type including neutrophils and mast cells. Filgrastim, pegfilgrastim and lenograstim are granulocyte colony stimulating factors (G-CSF) which stimulate production and differentiation of neutrophils from blood precursor cells.

Indications
Marketed: Reduction of the duration and clinical sequelae of neutropenia in patients with acute myeloid leukaemia, non-myeloid malignancy undergoing bone marrow transplant or myelosuppressive chemotherapy, Mobilisation of stem cells for subsequent autologous infusion after myeloablative or myelosuppressive treatment (filgrastim), Mobilisation of stem cells in donors for use in allogenic transplantation, Severe chronic neutropenia, Drug-induced neutropenia in HIV patients.

Accepted: Rescue treatment of drug-induced neutropenia (filgrastim), Chemotherapy-induced neutropenia (G-CSF), Drug-induced neutropenia (G-CSF), Autologous and allogenic bone marrow transplantation (G-CSF), Congenital, cyclic and idiopathic neutropenia (G-CSF), Myelodysplastic syndromes and aplastic anaemia (G-CSF), Stem cell mobilisation for autologous transplantation (ancestim with G-CSF).

Contraindications
Allergy to E. coli-derived proteins.
Administration with chemotherapy (24 hours before or after).

Specific considerations
Sickle cell disease: use with caution (use of G-CSF associated with sickle cell crisis).
Congenital neutropenia: possible increased risk of developing myelodysplasia and acute myeloid leukaemia.
Pregnancy: Contact specialised information service; ADEC category B3.
Breastfeeding: Contact specialised information service; limited data available.

Adverse effects
Adverse effects observed with filgrastim can be expected with pegfilgrastim although not all, especially the more uncommon, have been described.
Common: bone pain (dose-related), fever, splenomegaly (due to engorgement by cells produced).
Infrequent: chronic use may cause alopecia, haematuria, thrombocytopenia, exacerbation of pre-existing skin disorders (e.g. psoriasis), osteoporosis.
Rare: reactivation of autoimmune diseases, transient supraventricular arrhythmia, Sweet’s syndrome (acute febrile neutropenic dermatosis), capillary leak syndrome (pulmonary oedema, pericardial effusion, pericarditis), splenic rupture, toxic epidermal necrolysis, anaphylaxis.
Healthy donors: Serious adverse effects reported in healthy donors include cardiovascular disorders, MI, iritis, anaphylaxis, gouty arthritis and non-Hodgkins lymphoma.

There are long term safety concerns due to rare reports of malignancy, particularly myeloproliferative disorder and acute myeloid leukaemia; causal relationship not established. Prolonged follow up of donors is required to rule out late toxicity.

Dosage
According to specialist unit protocol. Usually 1–10 micrograms/kg daily or alternate days as SC injection or SC
infusion. The dose and duration of treatment are titrated according to patient response.

**Patient counseling**
Bone pain is a sign that the medication is working; use paracetamol or aspirin if needed.

**Practice points**
- in drug-induced neutropenia stop causative drug
- when used for drug-induced neutropenia in HIV patients, CD4, CD8 and natural killer T cell numbers increase, but there is no effect on mortality, hospitalisation or opportunistic infection rates
- monitor complete blood count before cytotoxic therapy and twice a week until recovery after nadir; monitor daily until recovery when using for other drug-induced neutropenia
- in severe chronic neutropenia monitor complete blood count twice a week for first month (and for 2 weeks after a dose change), then once a month for the first year when stable, then as required (those with congenital neutropenia also need annual bone marrow and cytogenetic evaluation)
- monitor for spleen enlargement and stop treatment if necessary (rare but serious risk of splenic rupture)
- monitor renal and liver function tests twice a week during treatment
- monitor cardiac function in patients with pre-existing cardiac conditions
- monitor healthy donors long term as serious adverse effects may develop
- round dosage to the nearest vial to avoid wastage (G-CSF product selection may be made on this basis).

**Products**
FILGRASTIM PFS 0.3 MCG/PFS (NEUPOGEN®, GESYSIN®, LEUCOSTIM®)

**08.05.02 OTHER DRUGS USED WITH ANTI NEOPLASTICS**

**CALCIUM FOLINATE**
Also known as calcium leucovorin, folic acid.

**Mode of action**
Bypasses inhibition of dihydrofolate reductase by folic acid antagonists, e.g. methotrexate, which otherwise results in inhibition of purine biosynthesis required for DNA production; this is also known as folic acid rescue. Competes for cellular uptake with methotrexate.
Fluorouracil modulator; enhances the inhibition of thymidylate synthetase, thereby increasing the cytotoxicity of fluorouracil.

**Indications**
Acute methotrexate poisoning.
Rescue treatment after methotrexate chemotherapy.
Gastric and colorectal cancer, advanced, with fluorouracil.
Toxicity associated with long term sulfadiazine or pyrimethamine therapy.

**Specific considerations**
- Pregnancy: Safe to use; ADEC category A.
- Breastfeeding: Safe to use.

**Adverse effects**
Infrequent: seizures, allergic reactions, fever.

**Dosage**
Acute methotrexate overdose: Start at 10 mg/m2 IV, but should be at least equivalent to the dose of methotrexate (in milligrams) ingested; subsequent doses need to be adjusted according to methotrexate concentration but may be up to 1000 mg/m2. Seek specialist advice from a Poisons Information Centre.
Methotrexate rescue: IV/oral, according to chemotherapy protocol: generally 50–100 mg IV followed by 15 mg (IV or oral) every 6 hours until methotrexate levels are below that recommended in protocol. Usually begins 24 hours after methotrexate administration.
Colorectal cancer (fluorouracil modulation): Consult specialist protocols. The following dose has been used with fluorouracil: 20 mg/m2 daily for 5 days, repeated every 4 weeks.
Toxicity associated with long term sulfadiazine or pyrimethamine therapy: Oral, 7.5–15 mg daily or 15 mg 3 times each week.
With pyrimethamine for toxoplasmosis during pregnancy: Oral, 15 mg daily.

**Practice points**
- folic acid is not an antidote for methotrexate or raltitrexed
- the time from acute methotrexate poisoning to administration of folic acid is critical to the outcome; begin treatment as soon as possible, preferably within the first hour and seek specialist advice
• calcium folinate 'rescue' is used to prevent or minimise myelosuppression or mucositis associated with methotrexate
• calcium folinate may occasionally be used with some antimicrobials to reduce the potential for haematological adverse effects (e.g. pyrimethamine when used for cerebral toxoplasmosis).

**Products**
CALCIUM CAPS OR TABS 15 MG (AS FOLINATE) (CALCIUM FOLINATE®, RESCUVOLIN®)

CALCIUM VIAL/AMP 50 MG/VIAL/AMP (AS FOLINATE) (CALCIUM FOLINATE®, LEUCOVORIN®, RESCUVOLIN®)

CALCIUM VIAL/AMP 100 MG/VIAL/AMP (AS FOLINATE) (CALCIUM FOLINATE®, RESCUVOLIN®)

**MESNA**
**Mode of action**
Contains free sulfhydryl groups which interact with urotoxic metabolites, including acrolein, of ifosfamide and cyclophosphamide and reduce the incidence of haemorrhagic cystitis and haematuria associated with these agents. Enhances urinary excretion of cysteine which may increase uroprotective effect.

**Indications**
Reduction and prevention of haemorrhagic cystitis and haematuria caused by cyclophosphamide or ifosfamide.

**Specific considerations**
Autoimmune disease: increased risk of allergic reaction.
Children: Limited experience of prophylactic use in infants and children indicates similar effects to use in adults.
Breastfeeding: Avoid use.

**Adverse effects**
Common: nausea, vomiting, diarrhoea, unpleasant taste, itch, rash, urticaria, facial oedema, headache, limb pain, hypotension.
Rare: hypertension.

**Dosage**
Mesna dose is calculated according to cyclophosphamide or ifosfamide dosage and the duration of the cytotoxic infusion. Mesna at total doses of 60–160% of the cyclophosphamide or ifosfamide dosage is given according to specialist protocols.

**Administration instructions**
IV, dilute to a final concentration of 1.5–3 mg/mL with 0.9% sodium chloride; may be given either over 15 minutes or as a continuous infusion.

**Patient counseling**
This drug does not treat cancer but is used to reduce the risk of bleeding from the bladder which sometimes occurs with cyclophosphamide and ifosfamide.
It is given by mouth or by injection during the time when you receive the cancer treatment.
It sometimes causes nausea and vomiting but this can usually be prevented with other medicines. Diarrhoea or rashes may also occur.

**Practice points**
• the duration of mesna treatment should equal that of the cytotoxic plus the time taken for the concentration of urotoxic metabolites in the urine to fall to nontoxic levels
• monitor urine for haematuria which may precede haemorrhagic cystitis; dose of mesna may be increased if urothelial toxicity occurs
• urine output should be maintained over 100 mL/hour in addition to mesna therapy
• mesna does not reduce antitumour effect of ifosfamide or cyclophosphamide
• may be used with regimens involving total body irradiation
• does not decrease haematuria associated with other conditions, e.g. thrombocytopenia.

**Products**
MESNA AMPS 400 MG/AMP 4 ML AMP (UROMITEXAN®)
Table 08-01 Comparison of oral/parenteral corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Routes</th>
<th>Potency</th>
<th>Duration of action (hours)</th>
<th>Equivalent anti-inflammatory oral or IV dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>IM, intra-articular, intradermal, soft tissue injection</td>
<td>25</td>
<td>36–54</td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>oral, IV, IM, intra-articular, soft tissue injection</td>
<td>0.8</td>
<td>8–12</td>
<td>25 mg</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>oral, IV, IM, intra-articular, soft tissue injection</td>
<td>25</td>
<td>36–54</td>
<td>0.75 mg</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>oral, IV, IM sodium succinate: IV, IM; acetate: IM, intra-articular, intradermal</td>
<td>1</td>
<td>8–12</td>
<td>20 mg</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>oral, IM, intra-articular, intradermal</td>
<td>5</td>
<td>12–36</td>
<td>4 mg</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>oral</td>
<td>4</td>
<td>18–36</td>
<td>5 mg</td>
</tr>
<tr>
<td>Prednisone</td>
<td>oral</td>
<td>3.5</td>
<td>18–36</td>
<td>5 mg</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>IM, intra-articular, intradermal</td>
<td>5</td>
<td>18–36</td>
<td></td>
</tr>
</tbody>
</table>

1 relates to glucocorticoid activity
2 relates to mineralocorticoid activity

Adapted from Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed. 2001.

Table 08-02 Comparative myelotoxicity of alkylating agents

<table>
<thead>
<tr>
<th>Alkylating agent</th>
<th>Effect on the bone marrow</th>
<th>Time to nadir</th>
<th>Time to recovery after nadir</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsacrine</td>
<td></td>
<td>neutrophils 12 days</td>
<td>14 days</td>
<td>pancytopenia may occur</td>
</tr>
<tr>
<td>Busulfan (&lt;8 mg/day)</td>
<td></td>
<td>neutrophils 10–30 days</td>
<td>up to 16 weeks</td>
<td>most prolonged pancytopenia</td>
</tr>
<tr>
<td>Busulfan (&gt;8 mg/day)</td>
<td></td>
<td>neutrophils 4 days, platelets 5–6 days after allogenic transplant</td>
<td>neutrophils 19 days, platelets 30 days</td>
<td>used with stem cell transplantation, red cell and platelet transfusion and granulocyte/stem cell colony stimulating factors</td>
</tr>
<tr>
<td>Carmustine</td>
<td></td>
<td>neutrophils 5–6 weeks, platelets 4–5 weeks</td>
<td>1–2 weeks</td>
<td>cumulative, prolonged myelosuppression may occur</td>
</tr>
<tr>
<td>Chlorambucil, continuous dose</td>
<td></td>
<td>neutrophils 10 days after last dose</td>
<td>1–2 weeks or longer</td>
<td>lymphopenia also occurs; cumulative doses of 6.5 mg/kg may cause irreversible myelosuppression</td>
</tr>
<tr>
<td>Chlorambucil, single high dose</td>
<td></td>
<td>neutrophils and platelets 7–14 days</td>
<td>1–2 weeks</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td>neutrophils 7–14 days</td>
<td>1–2 weeks</td>
<td>thrombocytopenia less common</td>
</tr>
<tr>
<td>Fotemustine</td>
<td></td>
<td>neutrophils 4–5 weeks, platelets 5–6 weeks</td>
<td>1–2 weeks</td>
<td>cumulative myelosuppression may occur</td>
</tr>
<tr>
<td>Treatment</td>
<td>Neutrophils effect</td>
<td>Platelets effect</td>
<td>Additional information</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>ifosfamide</td>
<td>7–14 days</td>
<td>3–10 days</td>
<td>Thrombocytopenia is less common</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(occasionally 2 weeks), 4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lomustine</td>
<td>Neutrophils 6 weeks</td>
<td></td>
<td>Cumulative myelosuppression may occur especially with prolonged therapy (&gt;1 year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets 1–2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>melphalan</td>
<td>Neutrophils and platelets 2–3 weeks</td>
<td>Platelets 3 weeks</td>
<td>Neutropenia may occur as early as 5 days after a dose; irreversible myelosuppression has occurred</td>
<td></td>
</tr>
<tr>
<td>temozolomide</td>
<td>Neutrophils 28 days, platelets 26 days</td>
<td>Platelets 2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thiotepa (15–30 mg)</td>
<td>Neutrophils and platelets 10–14 days or longer</td>
<td>Platelets 3 weeks</td>
<td>Pancytopenia has occurred; higher doses, e.g. 10 mg/kg, should be used with marrow support, e.g. granulocyte/stem cell colony stimulating factors; myelosuppression may occur with topical use</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 09 NUTRITION AND BLOOD

09.01 ANAEMIAS AND SOME OTHER BLOOD DISORDERS

09.01.01 IRON –DEFICIENCY ANAEMIAS

IRON DEFICIENCY ANAEMIA

Rationale for drug use
Prevent or reverse complications of anaemia and iron deficiency, including lethargy, dyspnoea and decreased effort capacity.

Before starting treatment
Establish that iron deficiency is the true cause of anaemia.
Assess for risk factors and possible causes:
- blood loss (GI, menorrhagia, NSAID use, blood donation)
- increased requirements (infants, adolescents, pregnancy, lactation)
- malabsorption (gastric surgery)
- inadequate diet (vegetarians, poor socioeconomic status)
- previous iron deficiency.
Treat correctable causes.

When to start treatment
Normal renal function, begin iron supplementation in anaemia (as measured by haemoglobin level) with iron deficiency (serum ferritin <15 micrograms/L).
Renal failure, give iron when anaemic and iron saturation is <20%.

Drug choice
Oral iron is the treatment of choice. Controlled release preparations are claimed to have fewer GI adverse effects, but may also have lower bioavailability. Parenteral iron is rarely indicated; reserve for malabsorption, noncompliance or when oral treatment is not possible, not tolerated, inadequate to meet demand or not effective (e.g. in patients on haemodialysis).

Other treatment
Blood transfusion may be necessary in severe anaemia.
Always give dietary advice for iron deficiency, with or without anaemia. Encourage increased intake of haem iron (red meat, chicken, fish), non-haem iron (grains and cereals, legumes, eggs, vegetables), and vitamin C to promote the absorption of non-haem iron (citrus fruit, broccoli, capsicum); avoid taking oral iron supplements with tea or coffee.

Special cases
Pregnancy: Routine iron supplementation is not recommended. Iron deficiency is associated with increased risk of preterm delivery, low birth weight, and delayed psychomotor development; however, evidence is lacking for the efficacy of iron supplementation in improving maternal and fetal outcomes. Give supplementation in women with low–normal haemoglobin where investigation shows iron deficiency.
Breastfeeding: Maternal iron supplements do not change the breast milk concentration of iron significantly; safe to use.

Duration of treatment
once haemoglobin concentration is normal, treat for a further 3 months to replenish iron stores

Practice points
- expect haemoglobin to rise 1–2 g/L daily, or 20 g/L over 3–4 weeks
- monitor haemoglobin for response to therapy; if no response detected in a month, review the diagnosis and consider noncompliance or coexisting problems, e.g. renal impairment, chronic inflammation, ongoing occult bleeding
- avoid unnecessary long term use of iron supplements.

09.01.01.01 ORAL IRON
IRON (FERROUS GLUTONATE, SULFATE)

Mode of action
Essential element required for the formation of haemoglobin and myoglobin.

Indications
Prevention and treatment of iron deficiency.
Treatment of iron deficiency anaemia in people on haemodialysis receiving epoetin.
Combination with folic acid: Prevention and treatment of iron and folate deficiency, particularly during pregnancy.

Contraindications
Haemochromatosis
Anaemia not due to iron deficiency
Allergy to parenteral iron (IM/IV)

Specific considerations
Transfusion-dependent anaemias: risk of iron overload; avoid iron supplementation.
GI disease: may be exacerbated by oral iron.
Pregnancy: Safe to use; ADEC category A.
Iron sucrose, no clinical data; ADEC category B3.
Breast feeding: Safe to use; maternal supplements do not significantly change the breast milk concentration of iron.
Iron sucrose, no clinical data.

Adverse effects
Common: Oral, abdominal pain, nausea, vomiting, constipation, diarrhoea (all dose-related), black discolouration of faeces.
Infrequent: IM, pain, inflammation and discolouration at injection site.
IV, taste change, nausea, vomiting, headache, arthralgia, myalgia, tachycardia, sweating, bronchospasm, hypotension, chest pain, rash, angioedema, Oral liquid, black discolouration of teeth.
Rare: IV/IM, anaphylaxis, Oral, GI erosion and perforation with high doses.
Overdose: Excessive iron intake (>20 mg/kg elemental iron) may result in toxicity (vomiting, diarrhoea, hypotension, tachycardia, acidosis, CNS depression). Treat with whole bowel irrigation; desferrioxamine may be necessary.
Iron overload (haemosiderosis) may occur with long term use of parenteral iron.

Dosage
All dosages below are expressed in terms of elemental iron.
1 mg elemental iron = approximately 9 mg ferrous gluconate = approximately 3 mg dried ferrous sulfate.
Prevention of iron deficiency anaemia: Child, oral, 1 mg/kg daily. Pregnancy, oral, 60–120 mg daily.
Treatment of iron deficiency anaemia: Oral, Adult, 100–200 mg daily. Child, 2–3 mg/kg daily; maximum 7 mg/kg daily.
Iron polymaltose: Dose according to manufacturer's product information or unit protocol. IM/IV 100 mg every 2 days until total dose administered.
Iron sucrose: IV infusion or slow injection over 15 minutes, 100 mg during dialysis session, no more than 3 times weekly. Most patients will require a minimum total dose of 1000 mg of elemental iron.
Combination with folic acid: 1 tablet or capsule daily.

Administration instructions
Iron polymaltose, follow administration instructions for IM use carefully to avoid pain and persistent skin discolouration.
Iron sucrose: give test dose before first administration.

Patient counseling
Accidental overdose (of even a small amount of an iron-containing product) can be very serious, even fatal, in children. Store out of reach and sight of children and keep bottles tightly closed.
This medicine is absorbed best if taken on an empty stomach 1 hour before, or 2 hours after, food. If it upsets your stomach, it can be taken with or shortly after food.
Dilute oral liquid with water and drink through a straw to prevent discolouration of teeth.

Practice points
- GI adverse effects may be reduced by starting at a low dose and gradually increasing, or by taking smaller doses more frequently
- controlled release preparations are claimed to have fewer GI adverse effects, but may also have lower bioavailability
- facilities for management of anaphylaxis should be available when using parenteral iron.
Ferrous Gluconate Tabs 300 mg (Ferroglucinate®, Glucofe®)
Ferrous Sulfate + Folic Acid + Zinc Sulfate Spansula (150 mg+0.5 mg+61.8 mg)
(Folifer-Z®)
Ferrous Sulfate + Folic Acid Spansula (150 mg+0.5 mg) (Fefol®, Feral®, Folifer®)
Ferrous Sulfate Tabs 325 mg (Ferrogard®)
Iron Oral Drops 10 mg/drop (Fersol®)
Iron Syrup 50 mg/5ml 100 ml Bottle (Not Registered)
Iron Amps 20 mg/amp (As Sucrose) (Venofe®)
Iron Amps 100 mg/amps (As Sorbitol) (Not Registered)

Iron Dextran
See Iron

Folic Acid
Mode of action
Required for synthesis of purine and pyrimidine bases (DNA) and for amino acid metabolism and normal erythropoiesis. Involved in the maturation of all rapidly proliferating tissues. Important for embryonic organogenesis, particularly neural tube closure.

Indications
Combination with iron, Prevention and treatment of iron and folate deficiency, particularly during pregnancy.
Accepted: Prevention of folate deficiency during chronic haemolysis and renal dialysis, Prevention of methotrexate adverse effects in treatment of rheumatoid arthritis and psoriasis.

Specific considerations
Anaemia of undiagnosed type: do not use folic acid alone.
Pregnancy: Safe to use; ADEC category A.
Breast feeding: Safe to use.
Adverse effects
Rare: rash, bronchospasm, fever, nausea, diarrhoea, irritability, sleep disturbance.

Dosage
Treatment of folate deficiency:
Adult, Oral, 5 mg once daily for at least 4 months. IM, 1–5 mg once daily.
Child, Oral, 0.5 mg/kg once daily; maximum 5 mg once daily.
Prevention of folate deficiency
Pregnancy: Low risk women (no family history of neural tube defects, not on antiepileptics), oral 500 micrograms daily before conception and continued for the first 12 weeks of pregnancy.
Previous pregnancy with neural tube defect, close family history of neural tube defects or women taking antiepileptics, oral 5 mg once daily before conception and continued for the first 12 weeks of pregnancy.
Chronic haemolysis and renal dialysis, Oral, 5 mg once daily to once a week, or 500 micrograms after dialysis.
With methotrexate in autoimmune disease, Oral, 1–5 mg once daily.

Practice points
- exclude vitamin B₁₂ deficiency before using folic acid to treat megaloblastic anaemia; high doses of folic acid can correct the anaemia of vitamin B₁₂ deficiency without preventing the associated neurological damage
- causes of folic acid deficiency include inadequate diet, malabsorption (gluten enteropathy, tropical sprue), increased utilisation (pregnancy, prematurity, malignancy, chronic haemolysis, myelofibrosis), increased loss (renal dialysis)

Iron Dextran Amps IV&IM (Not Registered)

09.01.02 Drugs Used in Megaloblastic Anaemia

Folic Acid
Mode of action
Required for synthesis of purine and pyrimidine bases (DNA) and for amino acid metabolism and normal erythropoiesis. Involved in the maturation of all rapidly proliferating tissues. Important for embryonic organogenesis, particularly neural tube closure.

Indications
Combination with iron, Prevention and treatment of iron and folate deficiency, particularly during pregnancy.
Accepted: Prevention of folate deficiency during chronic haemolysis and renal dialysis, Prevention of methotrexate adverse effects in treatment of rheumatoid arthritis and psoriasis.

Specific considerations
Anaemia of undiagnosed type: do not use folic acid alone.
Pregnancy: Safe to use; ADEC category A.
Breast feeding: Safe to use.
Adverse effects
Rare: rash, bronchospasm, fever, nausea, diarrhoea, irritability, sleep disturbance.

Dosage
Treatment of folate deficiency:
Adult, Oral, 5 mg once daily for at least 4 months. IM, 1–5 mg once daily.
Child, Oral, 0.5 mg/kg once daily; maximum 5 mg once daily.
Prevention of folate deficiency
Pregnancy: Low risk women (no family history of neural tube defects, not on antiepileptics), oral 500 micrograms daily before conception and continued for the first 12 weeks of pregnancy.
Previous pregnancy with neural tube defect, close family history of neural tube defects or women taking antiepileptics, oral 5 mg once daily before conception and continued for the first 12 weeks of pregnancy.
Chronic haemolysis and renal dialysis, Oral, 5 mg once daily to once a week, or 500 micrograms after dialysis.
With methotrexate in autoimmune disease, Oral, 1–5 mg once daily.

Practice points
- exclude vitamin B₁₂ deficiency before using folic acid to treat megaloblastic anaemia; high doses of folic acid can correct the anaemia of vitamin B₁₂ deficiency without preventing the associated neurological damage
- causes of folic acid deficiency include inadequate diet, malabsorption (gluten enteropathy, tropical sprue), increased utilisation (pregnancy, prematurity, malignancy, chronic haemolysis, myelofibrosis), increased loss (renal dialysis)
- drugs causing symptoms of folic acid deficiency include antiepileptics (barbiturates, phenytoin, carbamazepine), dihydrofolate reductase inhibitors (methotrexate, triamterene, trimethoprim, pyrimethamine) and sulfasalazine
- use IV folic acid only when oral administration is not possible
- folic acid decreases risk of elevated liver enzymes, and mucosal and GI adverse effects in patients receiving methotrexate for treatment of rheumatoid arthritis and psoriasis.

**Products**

**FOLIC ACID TABS 5 MG (FOLIC ACID®, FOLIC ACID HIKMA®, FOLIC 5®, VIFOLIN®, VITAFOL®)**

**VITAMIN B12, CYANOCOBALAMIN**

**VITAMIN B12, HYDROXOCOBALAMIN**

**VITAMIN B12, MECOBALAMINE**

**Mode of action**

Essential for nerve development, nucleic acid synthesis and normal erythropoiesis. There are 2 forms of vitamin B12 available, hydroxocobalamin and cyanocobalamin.

**Indications**

Prevention and treatment of vitamin B12 deficiency.

Treatment of optic neuropathies, e.g. tobacco amblyopia and Leber's optic neuropathy (hydroxocobalamin only).

**Specific considerations**

Pregnancy: Safe to use if indicated. Megaloblastic anaemia in pregnancy is usually due to folate deficiency.

Breastfeeding: Safe to use; should be given to lactating women who are strictly vegetarian (vegan).

**Adverse effects**

Rare: hypokalaemia and cardiac arrest (with high doses), allergy (including itch and anaphylaxis).

**Dosage**

The following doses apply to both adults and children.

Initial treatment of vitamin B12 deficiency: IM 1000 micrograms on alternate days for 1–2 weeks or until improvement occurs.

Prevention and maintenance treatment of vitamin B12 deficiency: Cyanocobalamin, IM 1000 micrograms once a month. Hydroxocobalamin, IM 1000 micrograms every 2–3 months.

Treatment of Leber's optic atrophy and tobacco amblyopia: Hydroxocobalamin, IM 1000 micrograms daily for 2 weeks, then twice a week for 4 weeks; maintenance IM 1000 micrograms once a month.

Prevention of vitamin B12 deficiency due to inadequate dietary intake: Cyanocobalamin, oral 100 micrograms twice daily.

**Administration instructions**

Do not give by IV injection.

**Practice points**

- causes of vitamin B₁₂ deficiency include pernicious anaemia, total or partial gastrectomy, ileal disease or resection, drugs, inadequate diet (vegan)
- confirm diagnosis and cause of vitamin B₁₂ deficiency before use; vitamin B₁₂ use may mask clinical and haematological features of folate deficiency
- do not use oral vitamin B₁₂ in cases of malabsorption
- pernicious anaemia or bowel resection requires lifelong treatment with vitamin B₁₂ injection
- IM hydroxocobalamin produces a greater and more sustained increase in serum vitamin B₁₂ than does the same dose of cyanocobalamin
- monitor potassium concentration during initiation of vitamin B₁₂ treatment, and correct hypokalaemia as needed
- monitor vitamin B₁₂ and blood count every year.
Products
VITAMIN B12, CYANOCOBALAMIN AMPS 1 MG/AMP (BETOLVEX®, CYANOCOBALAMIN®, CYTOBION®, OPTOVITE®)
VITAMIN B12, HYDROXOCOBALAMIN AMPS 1MG/AMP (AS ACETATE) (VIT B12®)
VITAMIN B12, MECOBALAMINE AMPS 500 MCG/AMP 1 ML AMP (METHYCOBAL®, PANCOBAMIN®)
VITAMIN B12, MECOBALAMINE TABS 500 MCG (COBAL®, METHYCOBAL®, NERVAMINE®, PANCOBAMIN®)

09.01.03 DRUGS USED IN HYPOPLASTIC, HAEMOLYTICS, AND RENAL ANAEMIAS

DESFERRIOXAMINE
Mode of action
Removes metals, in particular iron and aluminium, from the systemic circulation, by forming water-soluble complexes that are excreted in the urine.

Indications
Acute iron poisoning with either:
- peak serum iron (3–6 hours after ingestion) > 90 micromol/L (normal range 10–30) or 500 micrograms/dL (normal range 60–180)
- significant symptoms of iron toxicity (GI haemorrhage, acidosis, sedation, hypotension) and serum iron >60 micromol/L or serum iron not available.

Chronic iron overload (e.g. secondary to multiple transfusions, thalassaemia).

Contraindications
Allergy to desferrioxamine.

Specific considerations
Renal impairment: Use usual dose in dialysis patients as it is removed by dialysis.
Pregnancy: Avoid chronic use; benefits to mother would be expected to outweigh risks in acute poisoning; ADEC category B3.
Breastfeeding: No data available.

Adverse effects
Adverse effects vary with use, i.e. acute or chronic.
Common: Acute use, rashes, local irritation, hypotension, anaphylactoid reactions.
Infrequent: Acute use, anaphylaxis, non-cardiogenic pulmonary oedema, renal failure.
Rare: chronic use; bone marrow depression, growth retardation, ocular toxicity, ototoxicity.

Dosage
Acute iron overdose: Pretreat patients with IV sodium chloride 0.9% bolus (20 mL/kg).
15 mg/kg/hour by continuous IV infusion until serum iron is < 60 micromol/L; infusion rates > 15 mg/kg/hour in the first 24 hours may occasionally be advised by a clinical toxicologist in very severe or very high dose iron ingestion.

Chronic iron overload: Initial treatment requires specialist involvement,
Adult, child, maintenance in thalassaemia usually 1–3 g daily by slow SC infusion over 12–16 hours 4–6 times each week.

Practice points
- in acute iron poisoning it is important to maintain urine output to minimise risk of both nephrotoxicity and volume depletion, and to ensure that the iron–desferrioxamine complex is excreted; pretreat patients with an IV fluid bolus
- prolonged use of desferrioxamine (> 24 hours) may result in non-cardiogenic pulmonary oedema; monitor serum iron to assess need for continuing therapy
- for chronic iron overload, e.g. thalassaemia, start with the lowest daily dose and titrate to cause a negative iron balance; continue at that dose until the serum ferritin is within the normal range; then reduce the dose frequency to maintain normal serum ferritin
- SC route is preferred for chronic iron overload.

Products
DESFERRIOXAMINE VIAL 500 MG/VIAL (AS MESYLATED) (DESFERAL®)
ERYTHROPOEITIN (EPOETINS)

Mode of action
Recombinant glycoproteins which bind to erythropoietin receptors on erythroid progenitor cells. Stimulate erythropoiesis, increasing reticulocyte count, haematocrit and haemoglobin concentration.

Indications
Anaemia of chronic renal failure
Anaemia in non-myeloid malignancy where chemotherapy is used
Elective orthopaedic surgery with expected moderate blood loss in patients with moderate anaemia (haemoglobin 100–130 g/L)
Autologous blood collection before elective orthopaedic surgery in patients with anaemia
Anaemia of chronic renal failure
Anaemia in non-myeloid malignancy where chemotherapy is used
Elective orthopaedic surgery with expected moderate blood loss in patients with moderate anaemia (epoetin alfa)
Autologous blood collection before elective orthopaedic surgery in patients with anaemia (epoetin alfa)

Contraindications
Uncontrolled hypertension
Haemoglobin level >130 g/L (before surgery)
Surgical patients who cannot receive adequate antithrombotic treatment

Specific considerations
Hypertension: risk of aggravation.
Hepatic impairment
Safety and dose regime not established.

Pregnancy: Few data; use only if necessary; ADEC category B3.
Breastfeeding: Few data; use only if necessary.

Adverse effects
Common: hypertension (especially with rapid haemoglobin rise), headache, flu-like symptoms, bone pain, myalgia, fever, rash, hypotension, peripheral oedema, nausea, vomiting, diarrhoea, dyspnoea, increase in platelets, thrombosis of vascular access (patients on dialysis), local pain (with SC route)
Rare: seizures, allergic reaction, thrombotic events (MI, pulmonary embolism, stroke), pure red cell aplasia (epoetin alfa)

Dosage
Anaemia of chronic renal failure: Initial, IV 50 units/kg 3 times a week, increase or decrease by 25 units/kg/dose each month according to response. Increase dose if haemoglobin rise is <10 g/L in 4 weeks. Decrease dose by 25%–50% if haemoglobin rise is >25 g/L in 4 weeks. Maintenance, dose required to maintain haemoglobin at 100–115 g/L in 1–3 injections each week. Round dose to nearest syringe size. Maximum, 200 units/kg 3 times each week.
Elective orthopaedic surgery: SC 600 units/kg every week for 3 weeks before surgery and on day of surgery; or if less time before surgery, 300 units/kg daily for 10 days before surgery, on day of surgery and for 4 days after.
Autologous blood collection: IV 300–600 units/kg twice each week for 3 weeks.
Anaemia in non-myeloid malignancy receiving chemotherapy: SC initially, 150 units/kg 3 times a week for 4 weeks.
If haemoglobin increase <10 g/L or reticulocyte count <40 000 cells/microlitre, increase to 300 units/kg 3 times a week.
If haemoglobin increase >10 g/L per fortnight or >20 g/L per month or haemoglobin level close to 120 g/L, reduce dose by 25%–50%.
If haemoglobin level >120 g/L stop treatment until level <120 g/L and reinstitute at a dose 25% below the previous dose.

Patient counselling
Before injecting, hold syringe in hand for a few minutes to warm it (reduces pain).

Practice points
- use IV rather than SC route for epoetin alfa in patients with chronic renal failure as it has been shown to reduce the risk of pure red cell aplasia; use SC when IV access is not readily available
- use of epoetin alfa has been associated with increased mortality in a study in women with metastatic breast cancer; clinical significance of these findings is uncertain
- the risk of hypertension and seizures is minimised by aiming for haemoglobin increase around 10 g/L/month
- manage hypertension during the initial phase of treatment with antihypertensives and fluid removal if appropriate; reduce haemopoietic dose
• check iron, vitamin $B_{12}$ and folic acid status, and correct any deficiency; monitor iron status every month for 3 months, then every 3 months; nearly all patients will require iron supplement; give 200 mg elemental iron daily in elective surgery and autologous blood donation; IV iron is required in patients on haemodialysis
• monitor haemoglobin each week for first 8 weeks, then each month thereafter
• if response is inadequate, look for other causes of anaemia, including red cell aplasia, coexisting inflammation and infection
• urea, creatinine, phosphate and potassium concentrations may rise, possibly due to a combination of increased haemoglobin, decreased dialysis efficiency and general physical improvement with improved diet and exercise; these can be corrected with dietary modification, phosphate binders and adjustment of dialysis parameters; stop treatment until hyperkalaemia has been corrected

**Products**

ERYTHROPOEITIN ALFA VIAL 2,000 IU/VIAL (EPOETINS) (EPREX®, EPOKINE®, GEREPO®)
ERYTHROPOEITIN ALFA VIAL 4,000 IU/VIAL (EPOETINS) (EPREX®, EPOKINE®, GEREPO®)
ERYTHROPOEITIN ALFA VIAL 10,000 IU/VIAL (EPOETINS) (EPREX®)
ERYTHROPOEITIN BETA VIAL 2,000 IU/VIAL (EPOETINS) (RECORMON®)
ERYTHROPOEITIN BETA VIAL 4,000 IU/VIAL (EPOETINS) (NOT REGISTERED)
ERYTHROPOEITIN BETA VIAL 10,000 IU/VIAL (EPOETINS) (NOT REGISTERED)

**09.01.04 DRUGS USED IN NEUTROPENIA**

**FILGRASTIM**

**Mode of action**
Filgrastim is a recombinant stem cell factor which stimulates the growth of primitive progenitors which then can mature into any blood cell type including neutrophils and mast cells. Filgrastim, pegfilgrastim and lenograstim are granulocyte colony stimulating factors (G-CSF) which stimulate production and differentiation of neutrophils from blood precursor cells.

**Indications**
Marketed:
- Reduction of the duration and clinical sequelae of neutropenia in patients with acute myeloid leukaemia, non-myeloid malignancy undergoing bone marrow transplant or myelosuppressive chemotherapy.
- Mobilisation of stem cells for subsequent autologous infusion after myeloablative or myelosuppressive treatment.
- Mobilisation of stem cells in donors for use in allogenic transplantation.
- Severe chronic neutropenia.
- Drug-induced neutropenia in HIV patients.
- Accepted: Rescue treatment of drug-induced neutropenia.

**Contraindications**
- Allergy to *E. coli*-derived proteins.
- Administration with chemotherapy (24 hours before or after).

**Specific considerations**
- Sickle cell disease: use with caution (use of G-CSF associated with sickle cell crisis).
- Congenital neutropenia: possible increased risk of developing myelodysplasia and acute myeloid leukaemia.
- Pregnancy: contact specialized information centre; ADEC category B3.
- Breast feeding: Limited data available.
- Autoimmune and inflammatory conditions: may be exacerbated.
- Cardiac disease: risk of arrhythmia.
- Severe chronic neutropenia: may increase risk of myelodysplasia and acute myeloid leukaemia.

**Adverse effects**
- Common: bone pain (dose-related), fever, splenomegaly (due to engorgement by cells produced)
- Infrequent: chronic use may cause alopecia, haematuria, thrombocytopenia, exacerbation of pre-existing skin disorders (e.g. psoriasis), and osteoporosis.
- Rare: reactivation of autoimmune diseases, transient supraventricular arrhythmia, Sweet's syndrome (acute febrile neutrophenic dermatosis), capillary leak syndrome (pulmonary oedema, pericardial effusion, and pericarditis), splenic rupture, toxic epidermal necrolysis, and anaphylaxis.

Healthy donors: Serious adverse effects reported in healthy donors include cardiovascular disorders, MI, iritis, anaphylaxis, gouty arthritis and non-Hodgkin's lymphoma.
There are long term safety concerns due to rare reports of malignancy, particularly myeloproliferative disorder and
acute myeloid leukaemia; causal relationship not established. Prolonged follow up of donors is required to rule out late toxicity.

**Dosage**

According to specialist unit protocol. Usually 1–10 micrograms/kg daily or alternate days as SC injection or SC infusion. The dose and duration of treatment are titrated according to patient response.

**Patient counseling**

Bone pain is a sign that the medication is working; use paracetamol or aspirin if needed.

**Practice points**

- in drug-induced neutropenia stop causative drug
- when used for drug-induced neutropenia in HIV patients, CD4, CD8 and natural killer T cell numbers increase, but there is no effect on mortality, hospitalisation or opportunistic infection rates
- monitor complete blood count before cytotoxic therapy and twice a week until recovery after nadir; monitor daily until recovery when using for other drug-induced neutropenia
- in severe chronic neutropenia monitor complete blood count twice a week for first month (and for 2 weeks after a dose change), then once a month for the first year when stable, then as required (those with congenital neutropenia also need annual bone marrow and cytogenetic evaluation)
- monitor for spleen enlargement and stop treatment if necessary (rare but serious risk of splenic rupture).

**Products**

FILGRASTIM VIAL 300 MCG/VIAL (LEUCOSTIM®, GESYSIN®, NEUPOGEN®)

09.01.05 **ANTIFIBRINOLYTIC DRUGS AND HAEMOSTATICS**

**FACTOR VII A, ANTIHEAMPHILLIC, RECOMBINANT**

**Mode of action**

Plasma protein clotting factor which is absent or insufficient in individuals with haemophilia.

**Indications**

Prevention and treatment of bleeding associated with factor VII deficiency.

To treat bleeding episodes and to prevent bleeding associated with surgery in patients with haemophilia A or haemophilia B who have developed antibodies to factor VIII or factor IX, respectively.

Glanzmann's thrombasthenia.

Useful in patients with von Willebrand's disease.

**Specific considerations**

Allergic reaction or allergy to non-human mammalian protein (recombinant products)—use with caution.

Children: Safe to use.

Pregnancy: No data (symptomatic haemophilia A is very rare in women); ADEC category B2.

Breast feeding: No data; unlikely to be orally absorbed from breast milk.

Factor VIIa should be used with caution in patients with conditions associated with circulating tissue factor, such as advanced atherosclerosis, crush injury, or septicaemia, since there is a risk of precipitating thrombosis or disseminated intravascular coagulation.

**Adverse effects**

Minor skin reactions, fever, headache, and changes in blood pressure.

**Dosage**

Factor VIIa is given as the recombinant form, eptacog alfa (activated). Eptacog alfa (activated) 100 micrograms is equivalent to 5000 international units.

In the treatment of bleeding episodes in patients with haemophilia, an initial dose of eptacog alfa (activated) 90 micrograms/kg is given by intravenous bolus injection. Further doses may be given as required to achieve and maintain haemostasis, initially every 2 to 3 hours. The dose then be adjusted (effective doses have ranged from 35 to 120 micrograms/kg), or the dosing interval increased, according to response. Treatment may need to be continued for up to 3 weeks or more following serious bleeding episodes. A similar regimen may be used in patients with haemophilia when they undergo an invasive procedure or surgery, in which case the initial dose should be given immediately before the intervention.

In factor VII deficiency, the usual dose of eptacog alfa (activated) for treating bleeding episodes due to surgery or invasive procedures is 15 to 30 micrograms/kg every 4 to 6 hours until haemostasis is achieved.

In Glanzmann's thrombasthenia that is refractory to platelet transfusions, the usual dose of eptacog alfa (activated) for treating bleeding episodes or preventing bleeding due to surgery or invasive procedures is 90 micrograms/kg every 2 hours; at least 3 doses should be given.
FACTOR VII a, ANTIHEAMPHILLIC, RECOMBINANT VIAL 125 IU/VIAL (NOT REGISTERED)
FACTOR VII a, ANTIHEAMPHILLIC, RECOMBINANT VIAL 2.4 MG/VIAL (NOVOSEVEN®)

FACTOR VIII, ANTIHEAMPHILLIC
Includes highly purified plasma-derived factor VIII product and proteins produced by recombinant DNA technology, morococog alfa, octocog alfa and recombinant antihaemophilic factor.

Mode of action
Plasma protein clotting factor which is absent or insufficient in individuals with haemophilia A.

Indications
Prevention and treatment of bleeding associated with factor VIII deficiency (including haemophilia A or patients with factor VIII inhibitors), including perioperative management

Specific considerations
Allergic reaction or allergy to non-human mammalian protein (recombinant products): use with caution.
Children: Safe to use.
Pregnancy: No data (symptomatic haemophilia A is very rare in women); ADEC category B2.
Breast feeding: No data; unlikely to be orally absorbed from breast milk.

Adverse effects
Rare: headache, dizziness, nausea, sore throat, injection site reaction (erythema, rash, burning), allergic reaction including hypotension, urticaria, fever (may occur during infusion), intravascular haemolysis (only following very high doses of plasma-derived products due to blood group antibodies).
Antibody development: Factor VIII antibodies develop in up to 5–30% of patients with severe haemophilia during continued treatment, reducing the expected response to factor VIII.

Dosage
Required units = weight (kg) x desired factor VIII rise (% of normal) x 0.5.
Dosages below provide a guide for maintaining minimum factor VIII activity.
The desired factor VIII rise depends on the severity of the bleed. Higher dosages may be required when factor VIII inhibitors are present.
Mild bleed (e.g. superficial bleed), IV 10–15 units/kg.
Moderate bleed (e.g. haemarthrosis), IV 15–40 units/kg; repeat dose may be required in 12–24 hours.
Severe bleed (e.g. head injury, surgical procedure), IV 40–50 units/kg, followed by repeat doses of 20–25 units/kg every 8–12 hours until bleeding controlled; minor surgery, including dental extraction, usually requires only a single dose.

Practice points
- in mild haemophilia A (plasma factor VIII level at least 5% of normal) use desmopressin initially; use factor VIII if response to desmopressin is poor
- efficacy of different preparations of factor VIII appears similar
- consider vaccination against hepatitis A and B before using Biostate®; the possibility of transmission of viral infections and Creutzfeldt–Jakob disease, although low, cannot be ruled out
- adverse effects occurring during administration may respond to slowing infusion rate.

Products
FACTOR VIII, ANTIHEAMPHILLIC VIAL 250 IU/VIAL (DRIED FACTOR VIII®, FACTOR SDH®)
FACTOR VIII, ANTIHEAMPHILLIC VIAL 500 IU/VIAL (DRIED FACTOR VIII®, FACTOR SDH®)
FACTOR VIII, ANTIHEAMPHILLIC VIAL 1000 IU/VIAL (FACTOR SDH®)

FACTOR IX, ANTIHEAMPHILLIC
Includes a highly purified plasma-derived factor IX product and a protein produced by recombinant DNA technology.

Mode of action
Plasma protein clotting factor which is insufficient or abnormal in individuals with haemophilia B.

Indications
Prevention and treatment of bleeding in patients with haemophilia B, including perioperative management.

Specific considerations
History of disseminated intravascular coagulation, fibrinolysis, MI, liver disease: risk of thrombosis cannot be ruled out.
History of heparin-induced thrombocytopenia: risk of severe thrombocytopenia due to heparin content.
Pregnancy: contact specialized information centre; ADEC category B2.
Breast feeding: No data; unlikely to be orally absorbed.

**Adverse effects**
Rare: allergic reactions.

**Dosage**
Adjust dosage according to clinical condition and plasma factor IX concentrations.

**Adult**
Mild bleed (e.g. superficial bleed), IV 20–30 units/kg once daily for 1 or 2 days.
Moderate bleed (e.g. haemarthrosis), IV 30–50 units/kg once or twice daily for 1–5 days.
Minor surgery, initially, IV, 40–60 units/kg, and then 15–40 units/kg once or twice daily for 7–10 days.
Major surgery, initially, IV, 70–100 units/kg, then 20–90 units/kg once or twice daily for 10–12 days.

**Child: Prophylaxis**
IV, 25–40 units/kg twice each week.

**Administration instructions**
Inject slowly at 3 mL/minute.

**Practice points**
- the possibility of viral transmission, although low, cannot be ruled out; consider vaccination against hepatitis A and B before use
- antibodies to factor IX may develop rarely; patients with antibodies may be at increased risk of allergic reactions.

**Products**
- FACTOR IX, ANTIHEAMPHILLIC VIAL 250 IU/VIAL (NOT REGISTERED)
- FACTOR IX, ANTIHEAMPHILLIC VIAL 500 IU/VIAL (NOT REGISTERED)
- FACTOR IX, ANTIHEAMPHILLIC VIAL 1000 IU/VIAL (NOT REGISTERED)

**TRANEXAMIC ACID**
Antifibrinolytic

**Mode of action**
Inhibits breakdown of clots by blocking binding of plasminogen and plasmin to fibrin.

**Indications**
Prevention of hereditary angioedema.
Menorrhagia.
Hyphaema.

**Contraindications**
Active intravascular clotting.

**Specific considerations**
Predisposition to thrombosis: increases risk of thrombotic adverse effects.
Haematuria due to renal parenchymal disease: thrombosis may lead to intrarenal obstruction.
Subarachnoid haemorrhage: may increase cerebral ischaemic complications.
Renal impairment: Dose reduction required.
Pregnancy: contact specialized information centre; ADEC category B1.
Breast feeding: Safety not established.

**Adverse effects**
Common: nausea, vomiting, diarrhea.
Infrequent: hypotension, thrombosis.
Rare: transient disturbance of colour vision.

**Dosage**
Hereditary angioedema: 1–1.5 g 2–3 times daily either continuously or intermittently if aware of imminent onset of attack.
People with coagulopathies undergoing minor surgery
Cervical conisation, 1–1.5 g 2–3 times daily for 12 days postoperatively.
Prostatectomy, 1 g 6 hours preoperatively, then 1 g 3–4 times daily until macroscopic haematuria is no longer present (up to 2 weeks).
Dental surgery, 25 mg/kg 2 hours before surgery, and then 25 mg/kg 3–4 times daily for 6–8 days.
Hyphaema: 1–1.5 g 3 times daily for 6–7 days.
Menorrhagia: 1–1.5 g 3–4 times daily for 3–5 days during menses.

Renal impairment: Mild, 1 g twice daily. Moderate, 1 g daily. Severe, 500 mg daily.

Products

TRANEXAMIC ACID AMPS 500 MG/AMP 5 ML AMP (NOT REGISTERED)
TRANEXAMIC ACID TABS 500 MG (CYKLOKAPRON®)

09.02 FLUIDS AND ELECTROLYTES

09.02.01 ORAL PREPARATIONS FOR FLUID AND ELECTROLYTE IMBALANCE

POTASSIUM CHLORIDE (ORAL)

Potassium is an essential body electrolyte. However, requirements are difficult to determine and have been estimated from the amount accumulated during growth and reported urinary and faecal excretion.

Over 90% of dietary potassium is absorbed from the gastrointestinal tract. Potassium is particularly abundant in vegetables, potatoes, and fruit.

Indications

Compensation for potassium loss which is especially necessary:
- in those taking digoxin or anti-arrhythmic drugs, where potassium depletion may induce arrhythmia
- in patients in whom secondary hyperaldosteronism occurs, e.g. renal artery stenosis, cirrhosis of the liver, the nephritic syndrome, and severe heart failure
- in patients with excessive losses of potassium in the faeces, e.g. chronic diarrhea associated with intestinal malabsorption or laxative abuse.

Contraindications

Severe renal impairment.

Plasma potassium concentrations above 5 mmol/litre.

Specific considerations

Potassium salts should be given with considerable care to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. Excessive use of potassium-containing salt substitutes or potassium supplements may lead to accumulation of potassium especially in patients with renal insufficiency. Regular monitoring of clinical status, serum electrolytes, and the ECG is advisable in patients receiving potassium therapy, particularly those with cardiac or renal impairment.

Liquid or effervescent preparations are preferred to solid dosage forms for oral administration; use of the former, with or after food, may reduce gastric irritation. Solid oral dosage forms of potassium salts should not be given to patients with gastrointestinal ulceration or obstruction. They should be given with care to patients in whom passage through the gastrointestinal tract may be delayed, as in pregnant patients. Treatment should be discontinued if severe nausea, vomiting, or abdominal distress develops.

Potassium chloride should not be used in patients with hyperchloraemia.

Adverse effects

Hyperkalaemia

Cardiac toxicity is of particular concern after intravenous administration.

Pain or phlebitis may occur during intravenous administration via the peripheral route, particularly at higher concentrations.

Nausea, vomiting, diarrhoea, and abdominal cramps may occur following oral administration of potassium salts.

Gastrointestinal ulceration, sometimes with haemorrhage and perforation or with the late formation of strictures, after the use of enteric-coated tablets of potassium chloride.

Dosage.

2 – 4 gm (approx. 25 – 50 mmol) daily by mouth in patients taking a normal diet.

Smaller doses must be used if there is renal insufficiency (common in elderly).

Intravenous administration of a potassium salt is normally carried out by infusing a solution containing 20 mmol of potassium in 500 mL over 2 to 3 hours under ECG control. A recommended maximum dose is 2 to 3 mmol/kg of potassium in 24 hours. Adequate urine flow must be ensured and careful monitoring of plasma-potassium and other electrolyte concentrations is essential. Potassium chloride is the salt most commonly used and solutions intended for intravenous use that are in a concentrated form (such as 1.5 or 2 mmol/mL) must be diluted to the appropriate concentration before administration. There should be careful and thorough mixing when adding concentrated potassium chloride solutions to infusion fluids. Potassium chloride is also available as premixed infusions with sodium chloride and/or glucose containing 10 to 40 mmol/litre of potassium.
SODIUM BICARBONATE (ORAL)

Indications
Chronic acidotic states such as uraemic acidosis or renal tubular acidosis.
Increase the PH of the urine.
In dyspepsia as antacids.

Specific considerations
Bicarbonate or bicarbonate-forming compounds should not be given to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria. During treatment of acidosis, frequent monitoring of serum-electrolyte concentrations and acid-base status is essential.
Sodium-containing salts should be administered extremely cautiously to patients with heart failure, oedema, renal impairment, hypertension, eclampsia, or aldosteronism.

Adverse effects
Hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function. Symptoms include mood changes, tiredness, slow breathing, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop, especially in hypocalcaemic patients.
Excessive doses of sodium salts may also lead to sodium overloading and hyperosmolality.
Sodium bicarbonate given orally can cause stomach cramps, belching, and flatulence.

Dosage
In the treatment of chronic acidosis bicarbonate has been given by mouth and doses providing 57 mmol (4.8 g sodium bicarbonate) or more daily may be required.
In severe acidosis, sodium bicarbonate has been given intravenously by continuous infusion usually as a 1.26% (150 mmol/litre) solution or by slow intravenous injection of a stronger (hypertonic) solution of up to 8.4% (1000 mmol/litre) sodium bicarbonate.
Alkalisation of the urine: up to about 10 g daily in divided doses.
In antacid preparations: 1 to 5 g of sodium bicarbonate in water.

Products
SODIUM BICARBONATE TABS/CAPS 500 MG (SODIUM BICARBONATE TABS®, SODIUM BICARBONATE 500 CAPS®)

SODIUM CHLORIDE (ORAL)
The body contains about 4 mol (92 g) of sodium of which about one-third is found in the skeleton and about half is present in the extracellular fluid.
The body can adapt to a wide range of intakes by adjustment of renal excretion through physical and hormonal factors. Loss through the skin is significant only if excessive sweating occurs. Sodium requirements may be increased with exercise or exposure to high ambient temperatures in the short term, until the body adjusts.
Sodium is widely available in foods and is also added as salt during processing, cooking, and at the table. Dietary deficiency of sodium is therefore extremely rare and more concern has been expressed that current intakes are excessive. Restriction of sodium intake, by limiting the amount of culinary salt consumed, may be a useful aid in the management of some patients with hypertension.

Indications
Management of deficiencies of sodium and chloride ions in salt-losing conditions.
Sodium chloride solutions are used as a source of sodium chloride and water for hydration.

Specific considerations
Sodium salts should be used with caution in patients with hypertension, heart failure, peripheral or pulmonary oedema, renal impairment, pre-eclampsia, or other conditions associated with sodium retention.
When sodium supplements are given orally, adequate water intake should be maintained. Sustained-release tablets should not be given to patients with gastrointestinal disorders associated with strictures or diverticula because of the risk of obstruction.
Sodium chloride solutions should not be used to induce emesis; this practice is dangerous and deaths from resulting hypernatraemia have been reported.

Adverse effects
Hypernatraemia (a rise in plasma osmolality).
Accumulation of extracellular fluid to maintain normal plasma osmolality, which may result in pulmonary and peripheral oedema and their consequent effects. Gastrointestinal effects associated with acute oral ingestion of hypertonic solutions or excessive amounts of sodium chloride include nausea, vomiting, diarrhoea, and abdominal cramps. Excessive use of chloride salts may cause a loss of bicarbonate with an acidifying effect. The most serious effect of hypernatraemia is dehydration of the brain which causes somnolence and confusion progressing to convulsions, coma, respiratory failure, and death. Other symptoms include thirst, reduced salivation and lachrymation, fever, sweating, tachycardia, hypertension or hypotension, headache, dizziness, restlessness, irritability, weakness, and muscular twitching and rigidity.

**Dosage**
A 0.9% solution in water is iso-osmotic, and thus in most cases isotonic with serum and lachrymal secretions. Doses may be expressed in terms of mEq or mmol of sodium, mass (mg) of sodium, or mass of sodium salt. A typical oral replacement dose of sodium chloride in chronic salt-losing conditions is about 2.4 to 4.8 g (about 40 to 80 mmol of sodium) daily as a modified-release preparation, accompanied by a suitable fluid intake; doses of up to 12 g daily may be necessary in severe cases. Oral supplements are also used for the prevention of muscle cramps during routine haemodialysis; a suggested dose is about 6 to 10 g of a modified-release preparation per dialysis session.

Glucose facilitates the absorption of sodium from the gastrointestinal tract, and solutions containing sodium chloride and glucose usually with additional electrolytes are used for oral rehydration in acute diarrhoea. The concentration and dosage of sodium chloride solutions for intravenous use is determined by several factors including the age, weight, and clinical condition of the patient and in particular the patients’ hydration state. Serum-electrolyte concentrations should be carefully monitored. In severe sodium depletion, 2 to 3 litres of sodium chloride 0.9% may be given over 2 to 3 hours and thereafter at a slower rate. If there is combined water and sodium depletion a 1 to 1 mixture of sodium chloride 0.9% and glucose 5% may be appropriate. Although hypertonic sodium chloride solutions may be used in certain patients with severe acute dilutional hyponatraemia, over-rapid correction may have severe neurological adverse effects. Solutions containing 1.8 to 5% are available.

In hypernatraemia with volume depletion sodium chloride 0.9% may be used to maintain plasma-sodium concentrations with expanding fluid volume. Sodium chloride 0.9% (or rarely, in marked hypernatraemia, 0.45%) is used for fluid replacement in diabetic ketoacidosis.

**Products**
SODIUM CHLORIDE SACHETS 20 GM+SODIUM BICARBONATE 3.5 GM+POTASSIUM CHLORIDE 2.5 GM PER SACHETS (NOT REGISTERED)
SODIUM CHLORIDE TABS 0.5 GM (NOT REGISTERED)

**09.02.02 PARENTERAL PREPARATIONS FOR FLUID AND ELECTROLYTE IMBALANCE**

**09.02.02.01 ELECTROLYTES AND WATER**

**GLUCOSE (DEXTROSE) IV SOLUTION**
Glucose BP IS the monohydrate but Glucose Intravenous Infusion BP is a sterile solution of anhydrous glucose or glucose monohydrate, potency being expressed in terms of anhydrous glucose.

**Indications**
Treatment of carbohydrate and fluid depletion.
Used in oral rehydration solutions for the prevention and treatment of dehydration due to acute diarrhoeal disease.
Treatment of hypoglycaemia.
Given orally in the glucose tolerance test as a diagnostic aid for diabetes mellitus.

**Contraindications**
Glucose solutions is contra-indicated in patients with anuria, intracranial or intraspinal haemorrhage, and in delirium tremens where there is dehydration.
Should not be used after acute ischaemic strokes.

**Specific considerations**
Pregnancy: Glucose solutions are commonly employed as hydrating fluids and as vehicles for the administration of other drugs. It has been suggested that if used during labour the glucose load on the mother may lead to fetal hyperglycaemia, hyperinsulinaemia, and acidosis, with subsequent neonatal hypoglycaemia and jaundice. Others
have found no evidence of such an effect, especially if the fetus is well-oxygenated, and note that the number of patients included in such reports is often small and the selection criteria not homogeneous.

Stroke: Hyperglycaemia may be caused by physiological stress during ischaemic stroke, and this worsens cerebral ischaemic damage and impairs recovery. During cerebral ischemia, cellular hypoxia causes a shift from aerobic to anaerobic metabolism of glucose leading to intracellular lactic acidosis, which is toxic to the cell. Hyperglycaemia provides more glucose for anaerobic metabolism, further worsening intracellular acidosis. Blood-glucose concentrations should therefore be monitored and hyperglycaemia avoided or treated. Glucose infusions should not be used routinely after ischaemic stroke, unless specifically indicated. Hypoglycaemia must also be avoided and for patients who do require glucose, it should be administered by continuous infusion, avoiding large infusions or boluses that can cause hyperglycaemia.

Adverse effects
Local pain, vein irritation, and thrombophlebitis, and tissue necrosis if extravasation occurs.
Intravenous infusion can lead to the development of fluid and electrolyte disturbances including hypokalaemia, hypomagnesaemia, and hypophosphataemia. Prolonged administration or rapid infusion of large volumes of iso-osmotic solutions may cause oedema or water intoxication; conversely, prolonged or rapid administration of hyperosmotic solutions may result in dehydration as a consequence of the induced hyperglycaemia.

Dosage
Glucose solution 5% is the strength often employed for fluid depletion; it may be administered via a peripheral vein. Glucose solutions with a concentration greater than 5% are hyperosmotic and are generally used as a carbohydrate source; a 50% solution is often employed in the treatment of severe hypoglycaemia. Hyperosmotic solutions should generally be administered via a central vein although the American Hospital Formulary Service suggests that concentrations up to 10% may be administered via a peripheral vein for short periods provided the site is alternated regularly. In the emergency treatment of hypoglycaemia it may be necessary to use a peripheral vein but the solution should be given slowly; a suggested rate for glucose 50% in such circumstances is 3 mL/minute.
The dose of glucose is variable and is dependent on individual patient requirements; serum-glucose concentrations may need to be carefully monitored. The maximum rate of glucose utilisation has been estimated to be about 500 to 800 mg/kg per hour.
Strongly hyperosmotic glucose solutions (25 to 50%) have also been used to reduce cerebrospinal pressure and cerebral oedema caused by delirium tremens or acute alcohol intoxication although they do not appear to be widely employed. Glucose solution 50% has also been used as a sclerosing agent in the treatment of varicose veins and as an irritant to produce adhesive pleuritis in the management of pleural effusions and pneumothorax.
Ectopic pregnancy: Local instillation of 5 to 20 mL of glucose 50% into the gestational sac (salpingocentesis) has been described.

Hyperkalaemia: Insulin, together with glucose to prevent hypoglycaemia, is given to stimulate the cellular uptake of potassium in the emergency treatment of moderate to severe hyperkalaemia. Usually, 50 mL of glucose 50% is administered.

Hypoglycaemia: Glucose is used to correct insulin-induced hypoglycaemia, either by mouth or by infusion of a hypertonic solution (20 or 50%). Glucose 5 or 10% may be used but larger volumes are required.

Practice points
- glucose solutions should not be given through the same infusion equipment as whole blood as haemolysis and clumping can occur.

Products

- **GLUCOSE (DEXTROSE) IV SOLUTION 5 %** 500 ML BAG (DEXTROSE® (DIFFERENT COMPANIES))
- **GLUCOSE (DEXTROSE) IV SOLUTION 5 %** 1000 ML BAG
- **GLUCOSE (DEXTROSE) IV SOLUTION 10 %** 500 ML BAG
- **GLUCOSE (DEXTROSE) IV SOLUTION 10 %** 1000 ML BAG
- **GLUCOSE (DEXTROSE) IV SOLUTION 25 %** 500 ML BAG
- **GLUCOSE (DEXTROSE) IV SOLUTION 50 %** 500 ML BAG

**RINGER LACTATE**

Active Ingredients
- Sodium chloride 8.6 g
- Potassium chloride 0.3 g
- Calcium chloride 0.33 g
Water for injection to 1000 mL
Products
RINGER LACTATE SOLUTION (SODIUM CHLORIDE COMPOUND) 500 ML BAG (LACTATED RINGER®, LACTATED RINGER'S®, RINGER SOL®, RINGER'S SOLN®, RINGER'S INJ®, RINGER-LACTATE®)

RINGER LACTATE SOLUTION (SODIUM CHLORIDE COMPOUND) 1000 ML BAG (LACTATED RINGER®, LACTATED RINGER'S®, RINGER SOL®, RINGER'S SOLN®, RINGER'S INJ®, RINGER-LACTATE®)

SODIUM BICARBONATE
See Oral Sodium Bicarbonate
Products
SODIUM BICARBONATE VIAL 8.4 % 50 ML VIAL (SODIUM BICARBONATE 8.4%)

See Oral Sodium Chloride
Products
SODIUM CHLORIDE AMPS 0.9 % 20 ML AMP (SODIUM CHLORIDE® (DIFFERENT COMPANIES))
SODIUM CHLORIDE IV SOLUTION 0.18 % 500 ML BAG
SODIUM CHLORIDE IV SOLUTION 0.2 % 500 ML BAG
SODIUM CHLORIDE IV SOLUTION 0.45 % 500 ML BAG
SODIUM CHLORIDE IV SOLUTION 0.45 % + DEXTROSE 5 % 500 ML BAG
SODIUM CHLORIDE IV SOLUTION 0.9 % 500 ML BAG
SODIUM CHLORIDE IV SOLUTION 0.9 % 1000 ML BAG
SODIUM CHLORIDE IV SOLUTION 0.9 % + DEXTROSE 5 % 500 ML BAG
SODIUM CHLORIDE IV SOLUTION 0.9 % + DEXTROSE 5 % 1000 ML BAG
SODIUM CHLORIDE IV SOLUTION 18 % + DEXTROSE 5 % 500 ML BAG
SODIUM CHLORIDE IV SOLUTION 5 % 500 ML BAG

**09.02.02 PLASMA AND PLASMA SUBSTITUTES**

**ALBUMIN**

Mode of action
Albumin is the major protein involved in maintaining colloid osmotic pressure in the blood. It also binds a number of endogenous and exogenous substances including bilirubin, steroid hormones, and many, mainly acidic, drugs.

Indications
Albumin solutions are used for plasma volume replacement and to restore colloid osmotic pressure.
In conditions such as burns, severe acute albumin loss, and acute hypovolaemic shock.
As an exchange fluid in therapeutic plasmapheresis.
Concentrated albumin solutions are used in neonatal hyperbilirubinaemia associated with haemolytic disease of the newborn.
Short-term management of hypoproteinaemia in hepatic disease and in diuretic-resistant patients with nephrotic syndrome but are of little value in chronic hypoproteinaemias.

Contraindications
Cardiac failure.
Severe anaemia.

Specific considerations
History of cardiac or circulatory disease: administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function.
Increased capillary permeability
Correct dehydration when administering concentrated solution.
Injured or postoperative patients should be observed carefully following the administration of albumin as the rise in blood pressure may result in bleeding from previously undetected sites.

Adverse effects
Nausea and vomiting, increased salivation, and febrile reactions.
Allergic reactions, including severe anaphylactic shock. Rapid increases in circulatory volume can cause vascular overload, haemodilution, and pulmonary oedema.

**Dosage**

In acute hypovolaemic shock an initial dose of 25 g of albumin for adults (for example, 500 mL of a 5% solution or 100 mL of a 25% solution) and up to about 1 g/kg for children.

In hypoproteinaemia a maximum daily dose of 2 g/kg.

In neonatal hyperbilirubinaemia a dose of 1 g/kg before exchange transfusion.

A suggested rate of infusion is 1 to 2 mL/minute (5% solution) or 1 mL/minute (25% solution) although high rates may be needed in the treatment of shock.

**Practice points**

- if concentrated albumin solutions are to be diluted before administration, a suitable solution such as sodium chloride 0.9% or glucose 5% must be used
- there has been concern that albumin preparations may carry a potential risk of transmission of viral and subviral particles, notably Creutzfeldt-Jakob disease
- albumin solutions should not be used for parenteral nutrition
- plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient's condition at all times.

**Products**

ALBUMIN VIAL 10-20% 50 ML VIAL (ALBUMIN KABI®, HUMAN ALBUMIN VIAL®, HUMAN ALBUMIN INF®, HUMAN ALBUMIN INJ®)

DEXTAN 40

Dextrans of average molecular weight about 40 000.

**Indications**

Conditions associated with peripheral local slowing of the blood flow.

Prophylaxis of post-surgical thromboembolic disease.

**Contraindications**

Dextran 40 are contra-indicated in renal disease with oliguria.

**Specific considerations**

Dextran 40 may interfere with blood group cross-matching or biochemical measurements and these should be carried out before infusion is begun.

Plasma substitutes should be used with caution in patients with cardiac disease, liver disease, or renal impairment.

Correct dehydration beforehand, give adequate fluids during therapy and, where possible, monitor central venous pressure.

Pregnancy: avoid – reports of anaphylaxis in mother causing fetal anoxia, neurological damage and death.

**Adverse effects**

Hypersensitivity reactions such as fever, nasal congestion, joint pains, urticaria, hypotension, and bronchospasm.

Nausea and vomiting.

Rare: Severe anaphylactic reactions.

**Dosage**

Dextran 40 is given by intravenous infusion as a 10% solution in sodium chloride 0.9% or glucose 5%. Doses depend on the clinical condition of the patient.

In shock, a maximum of 20 mL/kg during the first 24 hours has been recommended; the first 10 mL/kg may be given by rapid intravenous infusion. Doses of up to 10 mL/kg may be given daily thereafter for up to 5 days. Dehydration should preferably be corrected before dextran 40 is administered.

In the treatment of thromboembolic disorders a suggested regimen is 500 to 1000 mL over 4 to 6 hours on the first day, then 500 mL over 4 to 6 hours on the next and subsequent alternate days for not more than 10 days.

For prophylaxis of postoperative thromboembolic disorders, 500 mL over 4 to 6 hours may be given during or at the end of surgery and the dose repeated on the next day; treatment may be continued in high risk patients on alternate days for up to 10 days.

Infants may be given up to 5 mL/kg and children up to 10 mL/kg.

A dose of 10 to 20 mL/kg has been added to extracorporeal perfusion fluids.
DEXTRAN 70
Dextrans of weight average molecular weight about 70,000.

Indications
Short-term blood volume expansion.
Prophylaxis of post-surgical thromboembolic disease.

Specific considerations
As for Dextran 40.

Adverse effects
As for Dextran 40.

Dosage
Dextran 70 is given by intravenous infusion as a 6% solution in sodium chloride 0.9% or glucose 5%.
Doses depend on the severity of the plasma loss and on the degree of haemoconcentration.
In shock, the usual initial dose for rapid expansion of plasma volume is 500 to 1000 mL infused at a rate of 20 to 40 mL/minute. A suggested maximum dose is 20 mL/kg during the first 24-hour period and 10 mL/kg per day thereafter; treatment should not continue for longer than 3 days. Patients may also require administration of blood, coagulation factors, and electrolytes.
For the prophylaxis of pulmonary embolism or venous thrombosis in moderate- to high-risk patients undergoing surgery, a dose of 500 to 1000 mL may be given over 4 to 6 hours either during or immediately after surgery. A dose of 500 mL should be given on the next day and in high-risk patients on subsequent alternate days for up to 2 weeks after the operation.
A 32% solution of dextran 70 has been instilled into the uterus in a dose of 50 to 100 mL as a rinsing and dilatation fluid to aid hysteroscopy.

HETASTARCH (ETHERIFIED STARCHES)
Etherified starches are starches that are composed of more than 90% of amyllopectin and that have been etherified to varying extents. In hetastarch (BAN, USAN) an average of 7 to 8 of the hydroxy groups in each 10 d-glucopyranose units of starch polymer have been converted into OCH2CH2OH groups.
Etherified starches also vary in terms of average molecular weight and the position of etherification within the glucopyranose unit.

Indications
Etherified starches are plasma volume expanders used in the management of hypovolaemic shock.
Hetastarch increase the erythrocyte sedimentation rate when added to whole blood. They are therefore used in leucopheresis procedures to increase the yield of granulocytes.

Specific considerations
Plasma substitutes should be used with caution in patients with cardiac disease, liver disease, or renal impairment.
Correct dehydration beforehand, give adequate fluids during therapy and, where possible, monitor central venous pressure.

Adverse effects
Hypersensitivity reactions may occur including, rarely, severe anaphylactic reactions.
Transient increase in bleeding time.
Pruritus.
Raised serum amylase.

Dosage
The dose and rate of infusion depend on the amount of fluid lost and degree of haemoconcentration; usual doses are in the range of 500 to 2500 mL daily, depending on the preparation used, and the infusion rate may be up to about 20 mL/kg per hour if necessary. Doses of 250 to 700 mL may be added to venous blood in the ratio 1 part to at least 8 parts of whole blood in such procedures. Up to 2 such procedures per week and a total of 7 to 10 have been reported to be safe.
MANNITOL SOLUTION

Mode of action
Mannitol is an osmotic agent. Although an isomer of sorbitol, it has little energy value, since it is largely eliminated from the body before any metabolism can take place.

Indications
Increase urine flow in patients with acute renal failure.
Reduce raised intracranial pressure.
Treat cerebral oedema.
Short-term management of glaucoma, especially to reduce intra-ocular pressure prior to ophthalmic surgery.
Promote the excretion of toxic substances by forced diuresis.
Bladder irrigation during transurethral resection of the prostate in order to reduce haemolysis and oral administration as an osmotic laxative for bowel preparation.

Contraindications
Congestive cardiac failure.
Pulmonary oedema.
Intracranial bleeding (except during craniotomy).

Specific considerations
Patients with renal failure: mannitol should not be given unless a test dose has produced a diuretic response (if urine flow is inadequate, expansion of the extracellular fluid may lead to acute water intoxication).
Mannitol should not be given with whole blood.
All patients given mannitol should be carefully observed for signs of fluid and electrolyte imbalance and renal function should be monitored.

Adverse effects
Fluid and electrolyte imbalance including circulatory overload and acidosis at high doses.
Pulmonary oedema and patients with diminished cardiac reserve are at special risk.
Tissue dehydration; dehydration of the brain, particularly in patients with renal failure, may give rise to CNS symptoms.
Diarrhea, nausea, vomiting, thirst, headache, dizziness, chills, fever, tachycardia, chest pain, hyponatraemia, dehydration, blurred vision, urticaria, and hypotension or hypertension.
Hypersensitivity reactions.
oedema and skin necrosis.
thrombophlebitis.

Dosage
The total dosage, the concentration, and the rate of administration depend on the fluid requirement, the urinary output, and the nature and severity of the condition being treated.
The usual adult dose of mannitol ranges from 50 to 100 g in a 24 hour period, given by intravenous infusion of a 5 to 25% solution. The rate of administration is usually adjusted to maintain a urine flow of at least 30 to 50 mL/hour.
For children, a dose of 0.25 to 2 g/kg has been used.
To reduce raised intracranial or intra-ocular pressure mannitol may be given by intravenous infusion as a 15 to 25% solution in a dose of 0.25 to 2 g/kg over 30 to 60 minutes.
During transurethral prostatic resection a 2.5 to 5% solution of mannitol has been used for irrigating the bladder.
09.05 MINERALS

09.05.01 CALCIUM AND MAGNESIUM

CALCIUM CARBONATE

Indications
Marketed: Calcium deficiency, Adjunctive treatment in osteoporosis, osteomalacia and rickets, Acute hypocalcaemia and hypocalcaemic tetany, Hyperphosphataemia associated with renal failure (as phosphate binding agent), Severe hyperkalaemia not due to digoxin toxicity. Magnesium toxicity, Hydrofluoric acid burns.

Accepted: Acute verapamil and diltiazem poisoning, Combination with cholecalciferol (vitamin D₃), Osteoporosis.

Contraindications
Hypercalcaemia.
Hypercalciuria.
Digoxin toxicity.

Specific considerations
Hyperparathyroidism: use cautiously as a phosphate binder in renal impairment (monitor calcium concentration).
Treatment with digoxin: combination may lead to arrhythmias; avoid using calcium injection solutions; monitor clinical effects, ECG and calcium concentrations if using oral calcium.
Treatment with calcitriol: increases risk of hypercalcaemia; avoid combination unless dietary intake is clearly inadequate.
Renal impairment: Monitor plasma calcium concentration; if necessary, reduce dosage or stop.

Pregnancy: Safe to use.
Breastfeeding: Safe to use.

Adverse effects
Common: belching, flatulence, abdominal distension, constipation.
Infrequent: hypercalcaemia, alkalosis, hypophosphataemia.
Rare: renal calculi, milk-alkali syndrome.
IV: skin necrosis (extravasation), irritation.

Milk-alkali syndrome: Presents acutely with headache, nausea, irritability and weakness or chronically with uraemia, alkalosis and hypercalcaemia; usually triggered by concomitant vomiting and/or sodium bicarbonate ingestion.

Dosage
Calcium deficiency, adjunctive treatment in osteoporosis, osteomalacia, rickets
Oral, adjust dose individually; the recommended daily intake of calcium for adults is 800 mg, 1100–1200 mg during pregnancy and lactation, and 1200–1500 mg in postmenopausal women.
Acute hypocalcaemia: IV, 2.25–4.5 mmol of elemental calcium (10–20 mL calcium gluconate injection 10%) by slow injection; then adjust according to plasma calcium concentration.
Hyperphosphataemia: Oral, 168–1200 mg elemental calcium (given as 420–3000 mg calcium carbonate) with each meal according to clinical response.
Combination with cholecalciferol (vitamin D₃) Oral, 1–2 tablets daily.

Administration instructions
Do not inject calcium solutions IM or SC as they are extremely irritating. Avoid extravasation during IV injection.

Patient counseling
Phosphate binder, if you skip a meal save your dose and take it when you next eat.

Practice points
- differences in formulation of calcium products (e.g. chewable tablet, effervescent tablet) may influence patient compliance.
09.05.02 PHOSPHORUS, SUPPLEMENTS AND BINDING AGENTS

GLYCINE + CALCIUM

Uses and Administration
Glycine is the simplest of the amino acids. It is used as a dietary supplement. Glycine is sometimes used with antacids in the treatment of gastric hyperacidity. It is also used as an ingredient of some aspirin preparations with the object of reducing gastric irritation.

Products
CALCIUM + GLYCINE TABS (420 MG+180 MG) (NOT REGISTERED)

POTASSIUM PHOSPHATE

Indications
Used in addition to vitamin D in patients with hypophosphataemic vitamin D-resistant rickets.
Alcohol dependence.
Phosphate deficiency.

Specific considerations
Monitor closely plasma concentrations of calcium, phosphate, potassium, and other electrolytes.

Adverse effects
Hypocalcaemia and metastatic calcification.

Dosage
In total parenteral nutrition regimens, it is necessary to provide adequate phosphate in order to allow phosphorylation of the glucose; between 20 and 30 mmol of phosphate is required daily.

Products
POTASSIUM PHOSPHATE AMPS (NOT REGISTERED)

SODIUM PHOSPHATE

As for potassium phosphate.

Products
SODIUM PHOSPHATE AMPS (NOT REGISTERED)

09.06 VITAMINES

09.06.02 VITAMIN-B GROUP

PYRIDOXINE (VITAMIN B6)

Mode of action
Coenzyme in numerous reactions; required for gamma-aminobutyric acid (GABA) synthesis (glutamate decarboxylase), homocysteine metabolism (cystathionine beta-synthase) and haemoglobin synthesis (ALA synthetase).

Indications
Marketed: Treatment and prophylaxis of pyridoxine deficiency including:
- acute isoniazid poisoning
- prevention of isoniazid-induced peripheral neuropathy
- pyridoxine-dependent seizures

Accepted: Sideroblastic anaemia, Homocystinuria.

Specific considerations
Pregnancy: Safe to use in therapeutic doses; exempted from ADEC categorisation.
Breast feeding: Safe to use.
Adverse effects
Infrequent: peripheral neuropathy (high dose), headache.

Dosage
Acute isoniazid overdose: Adult, child, seek specialist advice. Initial dose equal (mg for mg) to amount of isoniazid ingested or 5 g if amount unknown, given IV. Repeat dose after half an hour if seizures continue. Suspected pyridoxine-dependent seizures in infants: IV/IM/oral, 50–100 mg daily.
Adjunct to long term isoniazid therapy, homocystinuria: Adult, child, 25 mg daily.
Sideroblastic anaemia: Adult, 100–200 mg daily.

Practice points
- optimal dose of pyridoxine in acute isoniazid poisoning depends on dose of isoniazid ingested;
- benzodiazepines may be ineffective in stopping seizures when given without pyridoxine;
- some patients with sideroblastic anaemia will not respond to pyridoxine; stop treatment after a limited therapeutic trial (6–12 weeks) if this is unsuccessful;
- prolonged high doses of pyridoxine may be toxic and cause peripheral neuropathy; avoid unnecessary use.

Products
PYRIDOXINE (VITAMIN B6) AMPS 100 MG/AMP  2 ML AMP (NOT REGISTERED)
PYRIDOXINE (VITAMIN B6) TABS 40 MG (AS HCL) (PYRIDOXIN®)

VITAMIN B COMPLEX
Vitamin B group contains Thiamine (B1), Riboflavin (B2), Pyridoxine (B6), Cyanocobalamin (B12), and nicotinamide.

THIAMINE
Also known as vitamin B₁.

Mode of action
Coenzyme in carbohydrate metabolism.

Indications
Thiamine deficiency (beri-beri)
Ethylene glycol (eg antifreeze) poisoning
Prophylaxis of thiamine deficiency in high risk groups:
- alcohol misuse
- malnutrition
- severe malabsorption
- prolonged fasting (eg in intensive care units)
- total parenteral nutrition

Specific considerations
Pregnancy: Safe to use.
Breast feeding: Safe to use.

Adverse effects
Acute hypersensitivity reactions with parenteral administration

Dosage
100 mg IV/IM daily for at up to 5 days (if needed), then 100 mg orally daily.
For prevention of thiamine deficiency, continue daily dosing until the person is no longer at risk.
Ethylene glycol poisoning: 100 mg IV/IM every 6 hours until patient is well and acidosis has resolved.

Practice points
- absorption of oral thiamine may be impaired in many malnourished or alcoholic patients; give the first few doses parenterally (IM is preferred because there is less risk of an acute hypersensitivity reaction);
- patients regularly ingesting >60 g alcohol daily should be assumed to be at increased risk of thiamine deficiency; other features that may indicate increased risk are symptoms or history of alcohol withdrawal, a normal level of consciousness with a high blood alcohol concentration, or a raised GGT
- give parenteral thiamine before glucose to patients at risk of alcohol-related thiamine deficiency; administration of glucose before thiamine may precipitate Wernicke’s encephalopathy.
VITAMIN B COMPLEX AMPS  2-3 ML AMP (ANCOPIR®, NEUROBION®, TRI-B®)
VITAMIN B COMPLEX SYRUP   100 ML BOTTLE (BECOZYM®, VAROLEX®)
VITAMIN B COMPLEX TABS (ANCOPIR®, NEROVIT®, NEUROBION®, NEUROVITAN ®)

09.06.03 VITAMIN-C

VITAMIN C (ASCORBIC ACID)

Indications
Prevention and treatment of scurvy.

Dosage
Prophylaxis of scurvy: 25-75 mg daily.
Treatment of scurvy: 250 mg daily in divided doses.

Products
ASCORBIC ACID (VITAMIN C) AMPS 500 MG/AMPS (NOT REGISTERED)
ASCORBIC ACID (VITAMIN C) TABS 500 MG (VITA-C®)

09.06.04 VITAMIN-D

ALFACALCIDOL (VITAMIN D)

Mode of action
Regulate calcium homeostasis and bone metabolism. Increase intestinal absorption and renal reabsorption of calcium and phosphate. Promote bone mineralisation.

Indications
Prevention and treatment of vitamin D deficiency (osteomalacia in adults and rickets in children)
Hypocalcaemia in hypoparathyroidism, hypophosphataemic rickets, renal osteodystrophy, chronic renal dialysis
Treatment of osteoporosis
Prevention of corticosteroid-induced osteoporosis

Contraindications
Hypercalcaemia.

Specific considerations
Hyperphosphataemia: risk of ectopic calcification; restrict dietary phosphate and/or give phosphate binders.
Pregnancy: Safe to use at physiological doses; seek specialist advice for use at pharmacological doses; fetal risk with untreated maternal vitamin D deficiency may be greater than risk of vitamin D-related hypercalcaemia in the infant.
Breastfeeding: Safe to use at physiological doses; risk of hypercalcaemia in the infant at pharmacological doses.

Adverse effects
Most adverse effects are due to effects of hypercalcaemia; increased risk with calcitriol because of its high potency.
Early symptoms of hypercalcaemia include nausea, vomiting, constipation, anorexia, apathy, headache, thirst, sweating and polyuria.
Renal and cardiovascular damage may occur because of ectopic calcification.

Comparative information
Cholecalciferol and ergocalciferol
Have similar potency, a slow onset (4–8 weeks) and a prolonged duration of action (8–16 weeks).
Suitable for prevention and treatment of vitamin D deficiency due to inadequate sunlight or diet (eg elderly people, breastfed infants).
No risk of hypercalcaemia at physiological doses (eg <2000 units daily), except in rare instances, eg sarcoidosis.
Response to ergocalciferol and cholecalciferol depends on the ability of the kidney to hydroxylate them to produce the physiologically active hormone, calcitriol; do not use in patients with severe renal impairment.

Dosage
Vitamin D₂
Treatment of moderate-to-severe vitamin D deficiency: 75–125 micrograms (3000–5000 international units) daily for 6–12 weeks then 25 micrograms (1000 international units) daily.
Prevention of vitamin D deficiency, osteoporosis: 10–20 micrograms (400–800 international units) daily.
Dose equivalence: 1 international unit is equivalent to 0.025 micrograms.

Vitamin D₃
Prevention of vitamin D deficiency, 10–20 micrograms (400–800 international units) daily. The product available
contains 25 micrograms/tablet.

Dose equivalence: 1 international unit is equivalent to 0.025 micrograms.

**Patient counseling**

Do not take calcium supplements while taking this medicine unless your doctor tells you to.

Follow your doctor's dietary recommendations as sudden changes in your diet (especially the amount of dairy products) may increase the calcium in your blood.

Tell your doctor if nausea, vomiting, constipation, headache, frequent urination, thirst or tiredness develop.

Avoid taking other medications (including over-the-counter and health food preparations) that contain vitamin D.

**Practice points**

- dosage of 0.75 microgram daily is approved for prevention of corticosteroid-induced osteoporosis when corticosteroid dose is equivalent to >10 mg daily oral prednisolone, but there is a risk of hypercalcaemia and hypercalciuria at this dosage
- avoid calcium supplementation because of risk of hypercalcaemia, unless dietary intake is clearly inadequate
- adjust phosphate supplements in people with hypophosphataemic rickets.

**Monitoring**

- monitor plasma calcium concentration at baseline, twice during the first week, at 2–4 weeks, then every 2–3 months, and more often if indicated clinically, e.g. symptoms of hypercalcaemia
- stop treatment immediately if hypercalcaemia occurs
- monitor urinary calcium and phosphate concentrations periodically
- monitor more frequently in immobilised people and in patients with renal impairment.

**Products**

- **ALFACALCIDOL (VITAMIN D) AMPS 1 MCG/AMP (ONE ALPHA®)**
- **ALFACALCIDOL (VITAMIN D) AMPS 2 MCG/AMP (ONE ALPHA®)**
- **ALFACALCIDOL (VITAMIN D) CAPS 0.25 MCG (ONE ALPHA®)**
- **ALFACALCIDOL (VITAMIN D) CAPS 0.5 MCG (ONE ALPHA®)**
- **ALFACALCIDOL (VITAMIN D) CAPS 1 MCG (ONE ALPHA®)**

**CALCITRIOL**

- **CALCITRIOL AMPS 1 MCG/AMP 1 ML AMP (NOT REGISTERED)**
- **CALCITRIOL CAPS 0.25 MCG (BOCATORIOL®, ROCALTROL®)**

**09.06.05 VITAMIN A**

**RETINOL (VITAMIN A)**

**Mode of action**
Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision, particularly in dim light.

**Indications**
Treatment and prevention of vitamin A deficiency; Prolonged deficiency leads to xerophthalmia or 'dry eye', the initial symptom of which is night blindness which may progress to severe eye lesions and blindness. Other symptoms include changes in the skin and mucous membranes.

**Specific considerations**
Children and in patients with liver disease: Enhanced susceptibility to the effects of vitamin A may be seen.
Pregnancy: Excessive doses of vitamin A should be avoided in pregnancy because of potential teratogenic effects.
Cholestatic jaundice and fat-malabsorption conditions: Gastrointestinal absorption of vitamin A may be impaired in cholestatic jaundice and fat-malabsorption conditions so vitamin A supplements are often given to patients with primary biliary cirrhosis or chronic cholestatic liver disease as deficiencies are common in these disorders

**Adverse effects**
The administration of excessive amounts of vitamin A substances over long periods can lead to toxicity. Hypervitaminosis A (chronic toxicity) is characterised by fatigue, irritability, anorexia and loss of weight, vomiting and other gastrointestinal disturbances, low-grade fever, hepatosplenomegaly, skin changes (yellowing, dryness, sensitivity to sunlight), alopecia, dry hair, cracking and bleeding lips, anaemia, headache, hypercalcaemia, subcutaneous swelling, nocturia, and pains in bones and joints. Symptoms of chronic toxicity may also include raised intracranial pressure and papilloedema mimicking brain tumours, tinnitus, and visual disturbances which may be severe.
Acute vitamin A intoxication is characterised by sedation, dizziness, nausea and vomiting, erythema, pruritus, desquamation, and increased intracranial pressure (resulting in bulging fontanelle in infants).

**Dosage**
In universal distribution programmes, supplemental doses are given to all children up to the age of 5 at a dose of 200 000 units every 4 to 6 months, with infants between the ages of 6 and 12 months receiving half this dose. Infants aged less than 6 months may receive 50 000 units if they are not breast fed or if they are breast fed and their mothers have not received supplemental vitamin A. If clinical signs of vitamin A deficiency are evident at the time of routine supplementation, Mothers should receive 200 000 units within 6 weeks of delivery of a child. Targeted distribution programmes involve vitamin A supplementation to children and pregnant women in specific high-risk areas. Doses used in children are similar to those used in universal programmes, but doses used in pregnant women should not exceed 10 000 units' daily, or 25 000 units weekly.

**Products**
RETINOL (VITAMIN A) TABS 50,000 IU (A-VITON®, UNIVIT A®)

**09.06.06 VITAMIN-K**

**Phytomenadione (Vitamin K)**

**Mode of action**
Essential cofactor in the synthesis of blood clotting factors II, VII, IX and X, and proteins C and S; antagonist of oral anticoagulants.

**Indications**
Haemorrhage or threatened haemorrhage due to severe hypoprothrombinaemia, e.g. excessive oral anticoagulation, hypovitaminosis K.
Prevention and treatment of haemorrhagic disease of the newborn.

**Specific considerations**
Fat malabsorption syndromes, biliary atresia, pancreatic insufficiency—impaired oral absorption.
Pregnancy: Use if required; however, does not readily cross placenta; few data available.
Phytomenadione may be used from 36 weeks gestation in women taking liver enzyme-inducing antiepileptics (e.g. phenobarbitone, phenytoin and carbamazepine).
Breastfeeding: Safe to use.

**Adverse effects**
Common: pain, tenderness and erythema (IM injection).
Infrequent: allergic reactions including anaphylaxis (especially with rapid IV injection).
Rare: haemolytic anaemia, hyperbilirubinaemia, kernicterus (in neonates, especially if preterm).

**Dosage**
Reversal of oral anticoagulant effect: Slow IV/oral, 0.5–10 mg, depending on INR and presence of minor or major bleeding (see also Warfarin).
Prevention of haemorrhagic disease of the newborn: IM, 1 mg on day 1 postpartum; 0.5 mg in infants with a birth weight <1.5 kg. Oral, 2 mg given at birth, then at time of newborn screening (3–5 days of age) and in the fourth week; the last dose is not required in predominantly formula fed infants. Treatment of haemorrhagic disease of the newborn: slow IV, 1 mg; replacement of clotting factors and additional doses of vitamin K may be required.

**Administration instructions**
Can be given by mouth; tablets may be chewed.

**Practice points**
- vitamin K may not be required in all cases of excessive anticoagulation; temporarily stopping warfarin and readjustment of warfarin dose may be all that is necessary
- anticoagulant effect of warfarin may be difficult to re-establish for several days to weeks after large doses of vitamin K; if intending to restart warfarin, use lowest possible dose of vitamin K
- an extensive review of medical literature has concluded that there is no association between vitamin K and childhood cancer, regardless of the route of administration
- IM administration is the preferred route for prevention of haemorrhagic disease of the newborn because of reliability of administration and level of compliance; oral administration may be as effective as IM administration if there is full compliance with dosage schedule
- injection is commonly used orally for small doses needed to reverse oral anticoagulant effect.

**Products**
- PHYTOMENADIONE (VITAMIN K1) AMPS 1 MG/AMP (NOT REGISTERED)
- PHYTOMENADIONE (VITAMIN K1) AMPS 10 MG/AMP (PHYTOMENADIONE®, KONAKION®)

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**09.06.07 MULTIVITAMIN PREPARATIONS**

**MULTIVITAMIN (ORAL)**

Vitamins are natural substances that the body needs to grow, develop, and function normally. Vitamins are contained in food; a well-balanced diet usually provides all of the vitamins required. However, there are times, such as during pregnancy and childhood, when the body needs more vitamins than usual. During certain illnesses, the body either cannot get or cannot efficiently use all of the vitamins it needs.

Multivitamins are prescribed for patients who need extra vitamins, who cannot eat enough food to obtain the required vitamins, or who cannot receive the full benefit of the vitamins contained in the food they eat.

**Side effects**

Although side effects from multivitamins are not common, they can occur. Tell your doctor if either of these symptoms is severe or does not go away:
- upset stomach
- unpleasant taste

Before taking multivitamins,
- tell your doctor and pharmacist if you are allergic to multivitamins or any other drugs.
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially anticoagulants ('blood thinners') such as warfarin (Coumadin) and any other vitamins. Multivitamins are available in high-dose formulations (therapeutic multivitamins) and in combination with iron, calcium, and minerals. Do not take these formulations without your doctor's advice.
- tell your doctor if you are pregnant, plan to become pregnant, or are breast-feeding. If you become pregnant while taking multivitamins, call your doctor.

**Patient counselling**

This medication is sometimes prescribed for other uses; ask your doctor or pharmacist for more information.

Multivitamins come in regular tablets, chewable tablets, capsules, and oral liquid. They are usually taken once a day. Follow the directions on your prescription label or package label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take multivitamins exactly as directed.

If your vitamins come in a dropper bottle, use the specially marked dropper to measure each dose.

Your doctor will tell you if you need a specific type of vitamin product and how much to take. Some multivitamin preparations do not require a prescription. Ask your pharmacist for advice in selecting a multivitamin product and follow the directions on the label carefully.

Multivitamins come in regular tablets, chewable tablets, capsules, and oral liquid. They are usually taken once a day. Follow the directions on your prescription label or package label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take multivitamins exactly as directed.
If your vitamins come in a dropper bottle, use the specially marked dropper to measure each dose. Your doctor will tell you if you need a specific type of vitamin product and how much to take. Some multivitamin preparations do not require a prescription. Ask your pharmacist for advice in selecting a multivitamin product and follow the directions on the label carefully. Multivitamins come in regular tablets, chewable tablets, capsules, and oral liquid. They are usually taken once a day. Follow the directions on your prescription label or package label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take multivitamins exactly as directed. If your vitamins come in a dropper bottle, use the specially marked dropper to measure each dose. Your doctor will tell you if you need a specific type of vitamin product and how much to take. Some multivitamin preparations do not require a prescription. Ask your pharmacist for advice in selecting a multivitamin product and follow the directions on the label carefully.

Products
MULTIVITAMIN ORAL DROPS 10-30 ML BOTTLE (POLY-VIT®, POLY-VI-SOL®)
MULTIVITAMIN TABS (MULTI-VITAMINS (DIFFERENT COMPANIES))
MULTIVITAMIN TABS WITH MINERALS (MULTI-VITAMINS (DIFFERENT COMPANIES))
CHAPTER 10 MUSCULOSKELETAL DRUGS

10.01 DRUGS FOR OSTEOARTHRITIS, NSAIDs

OSTEOARTHRITIS

Rationale for drug use
Relieve symptoms (pain and stiffness) and improve joint function.

Before starting treatment
Advise on non-drug measures such as weight loss, activity (use it or lose it), physical therapy, devices (e.g. walking stick), and arthritis self-management courses.

When to start treatment
Consider drug treatment when patient requests symptoms relief.

Drug choice
Choose from topical preparations, paracetamol, NSAIDs, and intra-articular corticosteroids or hylans. By reducing symptoms they enable the patient to exercise and increase strength and mobility.

Paracetamol
Paracetamol is the preferred drug. It is better tolerated than an NSAID and may be as effective, especially if osteoarthritis is mild-to-moderate in severity.

Topical NSAIDs, capsaicin and rubefacients
These drugs can be used, but may be expensive. Local application has the advantage of lower systemic absorption and less frequent serious adverse effects. Topical NSAIDs are more effective than placebo, may be sufficient if symptoms are mild, and can be added to regular paracetamol if it is inadequate (may avoid the need for an oral NSAID).

NSAIDs
Serious adverse effects, including heart failure, renal impairment and GI bleeding are associated with all NSAIDs. No difference in efficacy has been demonstrated between different NSAIDs in the treatment of osteoarthritis. Addition of an NSAID to regular paracetamol may produce additive benefit and limit the dose of NSAID required. Choose a short acting agent (e.g. diclofenac), and aim for the lowest effective dose. Short courses of NSAIDs may provide benefit that can be maintained with simple analgesics. If NSAIDs are ineffective, contraindicated, or not tolerated, consider intra-articular corticosteroids or surgery.

Intra-articular corticosteroids
In placebo controlled trials, intra-articular corticosteroids provided little additional pain relief for osteoarthritis of the knee when compared to placebo (this could be due to the fact that draining effusion and administering the placebo injection had significant benefit itself). Possible adverse effects of intra-articular corticosteroids are local infections and acute inflammatory reaction.

Intra-articular hylans
Hylans are marketed for osteoarthritis of the knee. A course of 3–5 injections (at weekly intervals) can produce a small reduction in pain, when compared to placebo, which may last for several months. They may be an option when NSAIDs, intra-articular corticosteroids, or joint replacement surgery are contraindicated, and may be useful for patients waiting for joint replacement surgery.

Glucosamine
Commonly used to relieve osteoarthritic pain. It has been found to be as effective as an NSAID in some studies of osteoarthritis of the knee.

Two 3-year studies found that, in comparison to placebo, 1.5 g of glucosamine sulfate daily:
- is modestly effective in treating symptoms of osteoarthritis of the knee
- reduces radiological progression of the disease (no other treatment has shown this effect)
- has no effect on the use of rescue analgesics.

It is available from pharmacies and health food shops in a variety of salt forms, preparations, brands, and strengths, which may not be equivalent to the products used in the studies above. Some preparations are extracted from shellfish and contain traces of animal proteins; they should not be taken by people allergic to shellfish.

Treatment summary
- encourage regular exercise and non-drug measures (to reduce pain and increase strength and mobility)
- start drug treatment with regular paracetamol; continue non-drug measures
- if more analgesia is required, consider adding a topical NSAID, capsaicin or rubefacient
• if further analgesia is needed, add a low dose of a short acting NSAID, to be used only when needed (e.g. 30–60 minutes before painful activity); consider intra-articular corticosteroid or hylans
• if further analgesia is needed, use a higher dose of NSAID
• if this is inadequate, consider orthopaedic review and oral opioid analgesics, e.g. tramadol.

**Practice points**
• clinical signs of inflammation may not predict a better response to an NSAID than to paracetamol
• many patients on long term NSAID treatment can be switched to paracetamol without an increase in symptoms.

### 10.01.01 NONSELECTIVE NSAIDs (COX-1 AND COX-2 INHIBITORS)

#### DICLOFENAC

**Mode of action**
NSAIDs have analgesic, antipyretic, and anti-inflammatory actions. They inhibit synthesis of prostaglandins by inhibiting cyclo-oxygenase. Cyclo-oxygenase (COX) is present in 2 forms, COX-1 and COX-2. Inhibition of COX-1 is associated with impaired gastric cytoprotection and antiplatelet effects. Inhibition of COX-2 is associated with anti-inflammatory and analgesic action. Reduction in glomerular filtration rate and renal blood flow is associated with both COX-1 and COX-2 inhibition.

Most NSAIDs are nonselective, inhibiting both COX-1 and COX-2. Although selective COX-2 inhibitors have little or no effect on COX-1 at therapeutic doses, they are still associated with GI adverse effects.

**Indications**
Marketed: Symptomatic treatment of rheumatoid arthritis; symptomatic treatment of osteoarthritis; pain due to inflammation; dysmenorrhoea; postoperative pain; symptomatic treatment of local pain, and inflammation of soft tissues (topical).

Accepted:
- dysfunctional uterine bleeding.
- symptomatic relief of: Rheumatoid arthritis, including juvenile rheumatoid arthritis; other inflammatory arthropathies, e.g. ankylosing spondylitis, psoriatic arthritis, and Reiter's syndrome; Acute gout; dysmenorrhea; metastatic bone pain; and osteoarthritis
- headache and migraine; Postoperative pain; Mild-to-moderate pain due to inflammation and tissue injury; Fever; Renal colic.

**Contraindications**
Active peptic ulcer disease or GI bleeding.
Previous allergic reactions to NSAIDs, including aspirin.
Proctitis (suppositories).

**Specific considerations**
Asthma: may increase risk of bronchospasm (especially if there is also a history of rhinitis with or without nasal polyps).
Women planning pregnancy: may impair fertility (reversible).
Crohn's disease: may be exacerbated.
History of GI bleeding: avoid use of NSAIDs (including selective COX-2 inhibitors) if possible, or use with extreme caution.
Peptic ulcer: increased risk of GI ulceration.
Coagulation disorders: nonselective NSAIDs increase risk of bleeding (antiplatelet effect); selective NSAIDs appear to increase risk of thrombosis.
Bruising: further risk with topical NSAIDs.
Heart failure, hypertension: may be exacerbated by sodium and fluid retention caused by NSAID-induced reduction in glomerular filtration rate and renal blood flow.
Increased cardiovascular risk profile: selective NSAIDs (COX-2 inhibitors) may increase the risk of thrombotic events, e.g. MI and stroke (this led to withdrawal of rofecoxib).
Renal impairment: Increased risk of NSAID-induced renal impairment; nonselective NSAIDs increase risk of bleeding. Avoid use in moderate-to-severe impairment.
Hepatic impairment: Use with caution in severe impairment; nonselective NSAIDs increase risk of bleeding; selective NSAIDs (COX-2 inhibitors) are not recommended.
Surgery: There is a risk of renal impairment after surgery, especially if dehydration or renal hypoperfusion exists (as reduced renal blood flow increases the importance of intra-renal prostaglandins in maintaining renal function). There
is also an increased risk of bleeding with nonselective agents due to antiplatelet effects. Ensure that the patient is adequately hydrated before surgery, particularly when NSAIDs are to be used for postoperative analgesia. Consider type of surgery (laparoscopy and laparotomy particularly reduce renal blood flow), the dose of NSAID and its half-life. Stop NSAIDs 2–3 days before surgery, especially if there is a significant risk of postoperative bleeding, and in people requiring critical haemostasis. Selective NSAIDs (COX-2 inhibitors) do not affect platelet aggregation. Elderly: Increased risk of adverse effects, in particular heart failure, GI ulceration and renal impairment. Pregnancy: Two studies show a link between NSAID use during pregnancy and an increased rate of miscarriage. Risk appears highest when NSAIDs are taken around the time of conception. These agents inhibit prostaglandin synthesis; when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment and inhibition of platelet aggregation and may delay labour and birth. Continuous treatment with NSAIDs during the last trimester should only be given on sound indications. Avoid use during the last few days before expected birth; ADEC category C.

Lactation: Nonselective NSAIDs, safe to use. Selective NSAIDs (COX-2 inhibitors), limited data; appear safe.

Adverse effects
Common: nausea, dyspepsia, GI ulceration or bleeding, raised liver enzymes, diarrhoea, headache, dizziness, salt and fluid retention, hypertension.
Infrequent: oesophageal ulceration, rectal irritation (with suppositories), heart failure, hyperkalaemia, renal impairment, confusion, bronchospasm, rash. Topical use: skin irritation, erythema, itching, rash.
Rare: blood dyscrasias, interstitial nephritis, cystitis, nephrotic syndrome, acute renal failure, papillary necrosis, photosensitivity, Stevens–Johnson syndrome, epidermal necrolysis, hepatitis, aseptic meningitis, blurred vision, tinnitus, hypersensitivity (eg anaphylactic reaction, asthma, angioedema, urticaria).
Topical use—dyspnoea, nausea, dyspepsia, abdominal pain, gastritis, contact dermatitis, allergy, peripheral oedema.

Dosage
Adult: Oral or rectal, 75–150 mg daily in 2–3 divided doses. Maximum, 200 mg daily.
Child >6 months
Oral or rectal, 1–2 mg/kg/day in 2–3 divided doses. Up to 3 mg/kg/day may be used in juvenile chronic arthritis.
Postoperative pain in child >12 months, oral or rectal, initial dose 1–2 mg/kg, then 1 mg/kg 3 times daily for up to 3 days. Maximum 3 mg/kg/day.
Topical: Rub into the affected area 3–4 times daily.

Patient counselling
If you develop swollen ankles, difficulty in breathing, black stools or dark coffee-coloured vomit, stop taking the medicine and tell your doctor immediately.

Practice points
- only consider the diclofenac with misoprostol combination product for patients already stabilised on the same dose of single ingredient products because:
- the optimum dose of misoprostol to prevent NSAID-related gastric ulcers (800 micrograms daily) prevents use of the lowest effective dose of diclofenac
- misoprostol is poorly tolerated due to adverse effects (diarrhoea) and may lead to inadequate dose of NSAID
- about 60% of patients will respond to any NSAID; those who do not respond to one may respond to another; in osteoarthritis, maximal analgesic and anti-inflammatory effects are usually seen within 2 weeks; if appropriate responses are not observed within 3 weeks, try a different NSAID
- there is no rationale for using >1 NSAID at a time (excluding low dose aspirin); NSAIDs may be used with paracetamol or an opioid in the management of severe pain, eg tumour metastases in bone, or in the postoperative period
- seek specialist advice if a patient has aspirin-induced asthma and great need for an NSAID (may be able to tolerate a selective COX-2 inhibitor, with first dose given under medical supervision)
- do not stop low dose aspirin treatment when using an NSAID (NSAID antiplatelet effect is unreliable); there is no benefit in using a selective COX-2 inhibitor over nonselective agents in these patients
- measure complete blood count, creatinine and liver function before starting treatment, and repeat at least once a year during continued treatment
- to reduce GI complications:
  - use paracetamol as an alternative analgesic and/or to enable lower doses of NSAID
  - prescribe NSAID with a lower relative risk of GI complications, e.g. diclofenac
  - use the lowest effective dose for the shortest period of time
use one of the proton pump inhibitors or misoprostol, with an NSAID in high risk patients who must have an NSAID.

**Products**
DICLOFENAC AMPS 75 MG/AMP (AS SODIUM) 3 ML AMP (ALMIRAL®, DICLOGESIC®, INFLABAN®, ROFENAC®, URIGON®, VOLTAREN®, VOTREX®)
DICLOFENAC GEL 1 % (AS SODIUM) 30 GM TUBE (DICLOFEN®, DICLOVER®, DICLOGESIC®, LOCAGEL®, INFLABAN®, ROFENAC®, TABIFLEX®, VOLDIC®, VOTREX®)
DICLOFENAC SUPP. 12.5 MG (AS SODIUM) (DICLOFEN®, DICLOGESIC®, INFLABAN®, ROFENAC®, VOLDIC®, VOTREX®)
DICLOFENAC SUPP. 50 MG (AS SODIUM) (DICLOFEN®, DICLOGESIC®, DICLOSAL®, DICLOVER®, INFLABAN®, ROFENAC®, VOLDIC®, VOLTAREN®, VOTREX®)
DICLOFENAC SUPP. 100 MG (AS SODIUM) (DICLOFEN®, DICLOGESIC®, DICLOMAX®, DICLOTAB®, DIFEN®, INFLABAN®, JOFLAM®, NALGOFEN®) OLFEN®, OPTIFEN®, ROFENAC®, VOLDIC®, VOLTAREN®, VOTREX®)
DICLOFENAC TABS 25 MG (AS SODIUM) (ALMIRAL®, CLOFEN®, DICLOFEN®, DICLOGESIC®, DIFEN®, INFLABAN®, OLFEN®, OPTIFEN®, VOLTAREN®, VOTREX®)
DICLOFENAC TABS 50 MG (AS SODIUM) (ALMIRAL®, CLOFEN®, DICLOFEN®, DICLOGESIC®, DICLOMAX®, DICLOTAB®, DIFEN®, INFLABAN®, JOFLAM®, NALGOFEN®) OLFEN®, OPTIFEN®, ROFENAC®, VOLDIC®, VOLTAREN®, VOTREX®)
DICLOFENAC TABS 100 MG (AS SODIUM) (ALMIRAL®, DICLOFEN®, DICLOGESIC®, INFLANAN®, OLFEN®, OPTIFEN®, ROFENAC®, VOLDIC®, VOLTAREN®, VOTREX®)

**IBUPROFEN**

**Mode of action**
See under diclofenac.

**Indications**
See under diclofenac.

**Contraindications**
See under diclofenac.

**Specific considerations**
See under diclofenac.

**Adverse effects**
See under diclofenac.

**Dosage**
Adult: initially 1.2-1.8 g daily in 3-4 divided doses preferably after food; increased if necessary to max. 2.4 g daily; maintenance dose of 0.6-1.2 g daily may be adequate. Juvenile rheumatoid arthritis, child over 7 kg body weight 30-40 mg/kg daily in 3-4 divided doses. Fever and pain in children, child over 7 kg body weight 20-30 mg/kg daily in divided doses or 1-2 years 50 mg 3-4 times daily, 3-7 years 100 mg 3-4 times daily, 8-12 years 200 mg 3-4 times daily.

**Products**
IBUPROFEN SYRUP 100 MG/5ML 100 ML BOTTLE (BALKAPROFEN®, BRUFEN®, DOLORAZ®, IBUGESIC®, IBUPHIL®, IBUVER®)
IBUPROFEN TABS 200 MG (ADVIL®, BALKAPROFEN®, IBUGESIC®, IBURAM®, FLEXIMEX®, PEROFEN®, PROFINAL®, REMOFEN®, RUPAN®)
IBUPROFEN TABS 400 MG (BALKAPROFEN®, BRUFEN®, DOLORAZ®, IBUGESIC®, IBURAM®, FLEXIMEX®, MIDOFEN®, PEROFEN®, PROFINAL®, REMOFEN®, RUPAN®, TASKINE®)

**INDOMETHACIN**
Nonselective NSAID

**Mode of action**
See under diclofenac.

**Indications**
Rheumatoid arthritis; Osteoarthritis; Acute gout, Ankylosing spondylitis; Pain due to inflammation; Postoperative orthopaedic pain; Period pain; Closure of significant patent ductus arteriosus (injection, seek specialist advice)
Rheumatoid arthritis, including juvenile rheumatoid arthritis.

**Contraindications**
See under diclofenac.

**Specific considerations**
See under diclofenac.

**Adverse effects**
See under diclofenac; also vertigo.

**Dosage**
Adult: Oral, 25–50 mg 2–4 times daily. Rectal, 100 mg once or twice daily.
Child: Oral, 1–4 mg/kg daily in 2–4 divided doses.

**Products**
INDOMETHACIN CAPS 25 MG (INDOCID®, INDOGESIC®, INDOMIN®, INDLONY®, METHACIN®)
INDOMETHACIN CAPS/TABS 75 MG (INDOCID®, INDOGESIC®, BONDON®)
INDOMETHACIN SUPP. 100 MG (INDOCENT®, INDOCID®, INDOGESIC®, INDOMIN®, INDOPHARM®, METHACIN®)

**MEFENAMIC ACID**

**Mode of action**
See under diclofenac.

**Indications**
Period pain; Dysfunctional uterine bleeding; Pain due to inflammation.
Symptomatic relief of:
Rheumatoid arthritis; including juvenile rheumatoid arthritis; Other inflammatory arthropathies, e.g. ankylosing spondylitis, psoriatic arthritis and Reiter's syndrome; Acute gout; Period pain; Metastatic bone pain; Osteoarthritis
Headache and migraine; Postoperative pain; Mild-to-moderate pain due to inflammation and tissue injury
Fever; Renal colic.

**Contraindications**
See under diclofenac.

**Specific considerations**
See under diclofenac.

**Adverse effects**
Common: diarrhea, nausea, dyspepsia, GI ulceration or bleeding, raised liver enzymes, diarrhoea, headache, dizziness, salt and fluid retention, hypertension.
Infrequent: oesophageal ulceration, rectal irritation (with suppositories), heart failure, hyperkalaemia, renal impairment, confusion, bronchospasm, rash.
Topical use—skin irritation, erythema, itching, rash.
Rare: blood dyscrasias, interstitial nephritis, cystitis, nephrotic syndrome, acute renal failure, papillary necrosis, photosensitivity, Stevens–Johnson syndrome, epidermal necrolysis, hepatitis, aseptic meningitis, blurred vision, tinnitus, hypersensitivity (e.g. anaphylactic reaction, asthma, angioedema, urticaria). Topical use—dyspnoea, nausea, dyspepsia, abdominal pain, gastritis, contact dermatitis, allergy, peripheral oedema.

**Dosage**
Adult, 500 mg 3 times daily.
Child, 25 mg/kg daily in 3 divided doses (up to adult dose).

**Products**
MEFENAMIC ACID CAPS/TABS 500 MG (DYSMAN®, FENAMIC®, FENDOL DS®, PAINEX®, PANGESIC FORTE®, PONFAN®, PONSTAN FORTE®)

**NABUMETONE**
Nabumetone is a non-active prodrug whose major metabolite is an NSAID structurally similar to naproxen.

**Mode of action**
See under diclofenac.

**Indications**
Pain and inflammation in rheumatic disease (including juvenile arthritis) and other musculoskeletal disorders; dysmenorrhoea; acute gout.

**Contraindications**
See under diclofenac.

**Specific considerations**
See under diclofenac.
Adverse effects
See under diclofenac; also pulmonary fibrosis; pseudoporphyria characterised by blistering on the neck and hands;

Dosage
1 g by mouth taken as a single dose in the evening; if necessary 0.5 to 1 g may be given additionally in the morning. It has been recommended that a dose of 1 g daily should not be exceeded in elderly patients and that 500 mg daily may be satisfactory in some cases.

Products
NABUMETONE TABS 500 MG (NABUGESIC®, NABTON®)

NAPROXEN

Mode of action
See under diclofenac.

Indications
See under diclofenac.

Contraindications
See under diclofenac.

Specific considerations
See under diclofenac.

Adverse effects
See under diclofenac.

Dosage
Usual range
Conventional formulation, 250–500 mg twice daily.
Controlled release formulation, 750–1000 mg every 24 hours.
Maximum: 1250 mg daily.

Juvenile rheumatoid arthritis: 10–15 mg/kg daily in 2 divided doses.
Period pain: 500 mg initially, followed by 250 mg every 6–8 hours as required.
Migraine: 750 mg initially, followed by an additional 250–500 mg after at least 1 hour if necessary.

Dose equivalence
Doses above refer to naproxen. Naproxen sodium is used in some formulations. 500 mg naproxen is equivalent to 550 mg naproxen sodium.

Products
NAPROXEN SYRUP 125 MG/5 ML 100 ML BOTTLE (NOPAIN®, PROXIDOL®)
NAPROXEN TABS 250 MG (NOPAIN®, NOXEN®, PROXEN®)
NAPROXEN TABS 500 MG (NOPAIN DS®, NOXEN®, PROXEN®)

PIROXICAM

Mode of action
See under diclofenac.

Indications
Symptomatic treatment of rheumatoid arthritis.
Symptomatic treatment of osteoarthritis.
Symptomatic treatment of ankylosing spondylitis.
Symptomatic treatment of superficial sporting and similar injuries (topical).
Symptomatic relief of:
Rheumatoid arthritis, including juvenile rheumatoid arthritis; Other inflammatory arthropathies, e.g. ankylosing spondylitis, psoriatic arthritis and Reiter’s syndrome; Acute gout; Dysmenorrhoea; Metastatic bone pain;
Osteoarthritis
Headache and migraine; Postoperative pain; Mild-to-moderate pain due to inflammation and tissue injury
Fever; Renal colic.

Contraindications
See under diclofenac.

Specific considerations
See under diclofenac.

Adverse effects
See under diclofenac.
Dosage
Oral, 10–20 mg daily as a single dose with food.
Topical, apply to the affected area 3–4 times daily.

Products
PIROXICAM CAPS 20 MG (FELDENE®, PIROX®, REUCAM®, ROXAM®, UNICAM®)

TENOXICAM
Mode of action
See under diclofenac.

Indications
See under piroxicam.

Contraindications
See under diclofenac.

Specific considerations
See under diclofenac.

Adverse effects
See under diclofenac.

Dosage
Tenoxicam is given by mouth as a single daily dose usually of 20 mg. In acute musculoskeletal disorders treatment for up to 7 days is usually sufficient but in severe cases it may be given for up to a maximum of 14 days. Doses similar to those given by mouth have been given by intramuscular or intravenous injection for initial treatment for 1 to 2 days. Tenoxicam has also been given by rectal suppository.

Products
TENOXICAM TABS/CAPS 20 MG (TENOX®, TILCOTIL®)

10.01.02. SELECTIVE NSAIDs (COX-2 INHIBITORS)

MELOXICAM
Mode of action
Inhibits synthesis of prostaglandins by inhibiting COX-2.
Inhibition of COX-2 is associated with anti-inflammatory and analgesic action. Reduction in glomerular filtration rate and renal blood flow is associated with both COX-1 and COX-2 inhibition.

Indications
See under diclofenac.

Contraindications
See under diclofenac.

Specific considerations
See under diclofenac.

Adverse effects
See under diclofenac.

Dosage
Adult, 7.5–15 mg once daily, if required.

Practice points
• use the lowest effective dose for the shortest period of time, as the COX-2 selectivity of meloxicam is dose-dependent
• 15 mg provides greater pain relief than 7.5 mg, but also a higher frequency of GI adverse effects
• although partly (about 40%) metabolised by CYP2C9, adequate interaction studies have not been conducted; combination with CYP2C9 inhibitors is contraindicated.
10.02. DRUGS FOR RHEUMATOID ARTHRITIS

RHEUMATOID ARTHRITIS

Rationale for drug use
Provide relief of symptoms (pain and stiffness), maintain level of function, and prevent damage to bones, joints, and other organs.

Before starting treatment
Assess baseline function and joint damage, and consider prognosis.
Provide education about the disease and the protection of joints. Arrange appropriate physical and occupational therapy review.
Patients with rheumatoid arthritis (RA) are at increased risk of death due to cardiovascular disease compared to the general population. Look for and treat cardiovascular risk factors.
Consider immunization requirements (especially for live vaccines) before starting treatment that suppresses immune function.

When to start treatment
NSAIDs, simple analgesics and an antirheumatic drug can be started with the first symptoms of RA.
Refer to rheumatologist once diagnosis is made, as much of the joint damage occurs early in the disease, and treatment with a specific antirheumatic agent at this stage will retard progressive joint destruction and reduce long term disability.

Drug choice
Symptom relieving agents
Early disease: symptoms are best controlled by appropriate disease suppression (usually with a combination of a specific antirheumatic agent and analgesics or NSAID if needed).
Late disease: pain is often related to mechanical factors associated with established joint damage; paracetamol may be used instead of, or in addition to, NSAID.
NSAIDs: as any difference in efficacy between NSAIDs is small, choice is influenced by relative toxicity, duration of action (eg NSAID with long duration of action, taken in the evening, can help nocturnal and early morning symptoms) and the patient's response to treatment.

Corticosteroids
Early disease: low dose oral corticosteroids are well tolerated, may reduce erosions, and may be used to minimise disease activity before the specific antirheumatic agent's onset of effect. When stopping corticosteroids, reduce dose slowly to avoid rebound flare of symptoms
There is concern about long term adverse effects, eg osteoporosis, and difficulty in weaning patients from treatment.
Pulse (higher dose) oral, IM or IV corticosteroids can bring the disease under control rapidly but use is controversial. Symptomatic joints with synovitis—intra-articular corticosteroids can be used at any stage of the disease.

Specific antirheumatic agents
Include quinolines (hydroxychloroquine and chloroquine), immunosuppressants (methotrexate, azathioprine, cyclosporin and leflunomide), gold salts (aurothiomalate and auranofin), sulfasalazine and penicillamine. Onset of action is slow (usually 2–3 months) but varies between agents, eg 1–2 months with methotrexate, 2–6 months with hydroxychloroquine.
Choice of agent is influenced by disease severity (eg presence of active synovitis) and relative efficacy and toxicity of the drugs.
Mild disease: sulfasalazine or hydroxychloroquine are usually chosen first because they are less toxic than other antirheumatic agents. Sulfasalazine is more effective and acts sooner than hydroxychloroquine. Oral gold (auranofin) is used rarely as it is less effective and poorly tolerated (diarrhoea is common).
Moderate-to-severe disease: low dose methotrexate is the treatment of choice; it appears to be less toxic than other immunosuppressants, IM gold and penicillamine. Leflunomide is used for active disease when other specific antirheumatic agents (including methotrexate) are inappropriate or ineffective; recovery from adverse effects may be slow after stopping this drug because it has an active metabolite which has a long half-life.
In many cases a specific antirheumatic agent cannot control the disease completely. Combinations are commonly
used in an attempt to improve efficacy.

**Cytokine blockers**

Inflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor (TNF) alpha are involved in the pathogenesis of RA; they are also important in the immune defence against tumours and infection. TNF inhibitors (etanercept, infliximab, adalimumab): rapid onset of action compared to specific antirheumatic agents (can be within days). Used when antirheumatic agents are inadequate. Progression of joint damage is further slowed when they are used with methotrexate. TNF inhibitors increase susceptibility to serious infections; long term epidemiological studies are required to see if they also increase the risk of malignancy.

IL-1 antagonist (anakinra): like TNF inhibitors, anakinra is effective in RA refractory to treatment with specific antirheumatics, although it has a slower onset of effect. It is used with methotrexate.

**Practice points**
- some clinicians use corticosteroids to suppress disease in the period before specific antirheumatic agents start to act
- withdrawal of specific antirheumatic agents in apparent remission often results in relapse; some form of specific antirheumatic agent may need to be continued but, in remission, it may be possible to limit the use of the more toxic agents
- there is some evidence that, compared to placebo, daily supplements of 1.4–2.8 g of gamma-linolenic acid (present in evening primrose, borage seed and blackcurrant oils) taken for 6 months reduces the severity of symptoms such as number of tender joints, pain, swelling and stiffness.

**10.02.01 CYTOKINE BLOCKERS**

**ETANERCEPT**

**Mode of action**

Etanercept binds to tumour necrosis factor (TNF) and blocks its activity. TNF is an endogenous cytokine involved in normal inflammatory and immune responses and is found in increased concentrations in the synovial tissues in rheumatoid arthritis.

**Indications**

- Active rheumatoid arthritis with inadequate response to 1 or more specific antirheumatic agents (if necessary may be used with methotrexate).
- Severe rheumatoid arthritis with high risk of erosive disease (to slow progression of structural damage).
- Active and progressive psoriatic arthritis with inadequate response to specific antirheumatic agents.
- Active ankylosing spondylitis.
- Active polyarticular juvenile chronic arthritis in children 4–17 years with inadequate response to 1 or more specific antirheumatic agents.

**Contraindications**

- Allergy to etanercept.
- Sepsis or high risk of sepsis.
- Treatment with anakinra.

**Specific considerations**

- Infection or predisposition to infection: etanercept is associated with serious infection and sepsis, and may increase mortality in those with established sepsis; stop drug if serious infection develops during treatment.
- Demyelinating disorders, eg multiple sclerosis: may increase activity of disease.
- History of blood dyscrasias: rare cases of serious blood dyscrasias (some fatal) have been reported; monitor full blood count regularly during treatment with etanercept.
- Tuberculosis: may reactivate latent disease.
- Heart failure: may exacerbate condition.
- Surgery: Etanercept is associated with serious infections and sepsis; if the patient is to undergo major surgery, consider interrupting etanercept treatment until the risk of postoperative infection has declined.
- Children: Limited data available; etanercept has been studied in 69 children with juvenile rheumatoid arthritis (aged 4–17 years) for 3–7 months.
- Pregnancy: No data; avoid use; ADEC category B2.
- Lactation: No data; avoid use.

**Adverse effects**

- Common: injection site reaction (mild erythema, itching, pain or swelling), rash, allergic reactions (eg itching,
urticaria), upper respiratory tract infections (sinusitis, rhinitis, pharyngitis, cough), fever, autoimmune antibodies, headache, abdominal pain, dyspepsia.

Infrequent: thrombocytopenia.

Rare: serious infections, angioedema, anaphylaxis, seizures, systemic lupus erythematosus-like symptoms, cutaneous vasculitis, CNS demyelinating disorders, optic neuritis, anaemia, aplastic anaemia, leucopenia, pancytopenia.

**Dosage**

Rheumatoid or psoriatic arthritis, ankylosing spondylitis (adult), SC, 25 mg twice a week (3–4 days apart).

Juvenile chronic arthritis (4–17 years), SC, 0.4 mg/kg (maximum 25 mg) twice a week (3–4 days apart).

**Patient counseling**

Contact your doctor urgently if you develop persistent fever, sore throat, bruising, bleeding or pallor.

Some vaccines (such as oral polio vaccine) should not be given to people receiving etanercept. Check with your doctor before receiving any vaccines.

**Practice points**

- seek specialist advice if a patient is exposed to chickenpox or shingles during therapy; consider use of zoster immunoglobulin,
- measure complete blood count before starting treatment and if symptoms suggesting infection or blood dyscrasias occur during treatment; stop etanercept if serious infections develop or blood dyscrasias are confirmed
- data on safety and efficacy of treatment >24 months are not available
- the effect of long term treatment on the development of autoimmune diseases is unknown; it is of concern since etanercept treatment commonly results in the formation of autoimmune antibodies
- benefit may be seen after approximately 1–12 weeks of treatment.

**Products**

ETANERCEPT 25 MG POWDER/VIAL (ENBREL ®)

### 10.02.02 IMMUNOSUPPRESSANTS

**LEFLUNOMIDE**

**Mode of action**

Inhibits pyrimidine synthesis in leucocytes and other rapidly dividing cells by inhibiting activity of dihydro-orotate dehydrogenase. It has immunosuppressive, immunomodulating and antiproliferative properties. Also has uricosuric effects.

**Indications**

Active rheumatoid arthritis in adults.

**Contraindications**

Previous allergic reaction to leflunomide.

Pregnancy.

Severe infection.

Hepatic impairment or moderate-to-severe renal impairment.

History of Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.

Severe immunodeficiency states or bone marrow depression (eg anaemia, leucopenia, thrombocytopenia) not due to rheumatoid arthritis.

**Specific considerations**

Infections: leflunomide-induced immunosuppression may increase risk and severity of infection. If a severe infection occurs it may be necessary to stop leflunomide and hasten its elimination.

Women of child-bearing potential: only use if reliable contraceptive methods are being used.

Concurrent methotrexate and/or other hepatotoxic drugs: increased risk of serious hepatic reactions; avoid if possible; otherwise monitor each month.

Surgery: No data in humans (delayed healing of corneal lesions in dogs).

Pregnancy: Contraindicated; teratogenic in animals (no human data); its active metabolite has a long half-life (2–4 weeks) and a lengthy period after stopping this drug (about 2 years) is needed before a planned pregnancy (for shorter elimination procedure). ADEC category X.

Lactation: Excreted in breast milk, no other data available; do not breastfeed.

**Adverse effects**

Common: abdominal pain, diarrhoea, nausea, vomiting, cholelithiasis, raised liver enzymes, hair loss, rash, itching,
eczema, weight loss, synovitis, tenosynovitis, headache, dizziness, paraesthesia, bronchitis, pharyngitis, pneumonia, hypertension.

Infrequent: constipation, oral thrush, stomatitis, taste disturbance, transient thrombocytopenia.

Rare: anaphylaxis, angioedema, anaemia, eosinophilia, agranulocytosis, leucopenia, pancytopenia, serious skin reactions (eg toxic epidermal necrolysis, Stevens–Johnson syndrome), severe infection, respiratory disorders (eg dyspnoea, interstitial pneumonitis), hepatic cirrhosis, liver failure.

Hepatic reactions: Transaminase concentrations are commonly raised at the start of treatment; these effects are usually mild and resolve while continuing. Rare cases of severe hepatic injury (some fatal), have been reported; most occurred within 6 months of starting treatment.

**Dosage**

Loading dose, 100 mg once daily for 3 days.

Maintenance dose, 20 mg once daily. If poorly tolerated, reduce dose to 10 mg daily.

**Patient counselling**

Contact your doctor urgently if you develop mouth ulcers, skin problems, persistent fever, sore throat, unusual tiredness, bruising, bleeding, paleness, abdominal pain or yellowing of the skin (jaundice).

Do not drink alcohol during treatment because it may increase the risk of liver damage which is a rare side effect with this medicine.

Some vaccines (such as oral polio vaccine) should not be given to people receiving leflunomide. Check with your doctor before receiving any vaccines.

**Practice points**

- leflunomide has an active metabolite with a long half-life (2–4 weeks) therefore:
- a loading dose is needed so that steady state plasma concentration (and effectiveness) is reached as quickly as possible (without loading this could take 2 months)
- adverse effects may be prolonged after stopping the drug; consider using washout procedure
- in trials, clinical improvement usually started after about 4 weeks of treatment and stabilised within 4–6 months.

**Patient monitoring**

- before starting treatment measure BP, complete blood count, renal and liver function (ALT), and hepatitis B and C serology in high risk patients
- monitor complete blood counts every 2 weeks for the first 6 months, then every 8 weeks
- monitor ALT and creatinine each month for the first 6 months, then every 8 weeks (or more frequently as determined by the clinical situation, eg monitor each month if using with methotrexate)
- if ALT >3 times the upper level of normal stop drug; use washout procedure
- if ALT between 2 and 3 times the upper level of normal, consider reducing dose from 20 mg to 10 mg; measure ALT each week (if ALT persistently >twice the upper level of normal stop drug; use washout procedure).

**Washout procedure**

- give 8 g cholestyramine 3 times daily (or 50 g activated charcoal 4 times daily) for 11 days (duration may be modified depending on clinical or laboratory variables, seek specialist advice).

**Products**

LEFLUNOMIDE TABS 10 MG (ARAVA®)
LEFLUNOMIDE TABS 20 MG (ARAVA®)

**TRIAMCINOLONE (SKIN)**

**Mode of action**

Anti-inflammatory, immunosuppressive and antimitotic activity against cutaneous fibroblasts and epidermal cells. They are also vasoconstrictive.

**Indications**

Inflammatory skin conditions. Relief of inflammation and itch in conditions such as eczema and psoriasis.

**Contraindications**

Rosacea.
Acne vulgaris.
Allergy to product ingredients.
Ulcerative skin conditions or impaired circulation.
Uncontrolled infection in area to be treated.
Specific considerations
Skin atrophy: increases systemic absorption and skin atrophy worsens; avoid use.
Diabetes: systemic absorption increases blood glucose concentration; avoid extensive use.
Impaired T cell function: systemic absorption results in immunosuppression; avoid extensive use.
Elderly: Skin atrophy makes cutaneous adverse effects more likely.
Children: Increased systemic absorption due to higher surface area/weight ratio. Skin permeability increased in neonates and infants.

Hydrocortisone is adequate initial treatment for most children with mild-to-moderate disease. Use more potent preparations for short periods under close supervision to regain control of disease.

Consider a corticosteroid-free period of at least 2 weeks after each 2–3-week period of daily use.

Pregnancy: Use the lowest appropriate potency of topical corticosteroid for the shortest time necessary where emollients and other simple measures are inadequate; betamethasone, hydrocortisone, methylprednisolone and triamcinolone ADEC category A; desonide and mometasone ADEC category B3 (safety data are lacking, use others in preference).

Breastfeeding: Safe to use; ensure breast area is free of corticosteroid before breastfeeding.

Adverse effects
Relative potency, patient age, site and extent of disease, preparation type, method of application and length of treatment determine the incidence and severity of adverse effects.

Common: folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, striae, purpura, depigmentation, telangiectasia.

Infrequent: allergic contact dermatitis.

Rare: hyperaesthesia, subcutaneous tissue atrophy, systemic effects (growth retardation, hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, Cushing's syndrome, cataract).

Dosage
Apply a thin layer 1–2 times a day.

Patient counselling
Apply a thin layer by smoothing gently into skin, preferably after bathing.

Practice points
- use an appropriately potent preparation for the shortest time necessary to control skin disorder, then stop corticosteroid
- wet wrap treatment may be useful in acute eczema
- occlusion with polythene films may be used on the palms and soles or on limited areas of lichenification; use vinyl gloves for hands
- avoid tolerance by applying corticosteroid on alternate days or using medication-free periods (e.g. 5 days on then 2 days off) during treatment of chronic dermatoses
- potential for systemic absorption increases with extent and activity of disease; monitor strength and amount being used.

Products
TRIAMCINOLONE VIAL 40 MG/VIAL (AS ACETONIDE) (KENACORT A®; PANBICORT®)

10.02.03 QUINOLINES

HYDROXYCHLOROQUINE
Mode of action
Anti-inflammatory. May also have immunosuppressive effects.

Indications
Marketed: Rheumatoid arthritis (mild); Discoid and systemic lupus erythematosus; Prophylaxis and treatment of malaria if chloroquine is not available.
Accepted: Juvenile rheumatoid arthritis, >6 years of age; Rheumatoid arthritis (mild); Discoid and systemic lupus erythematosus; Malaria prophylaxis and treatment.

Contraindications
Retinopathy.
Pregnancy (except for malaria prophylaxis).
Children <6 years.
Allergy to a quinoline.
Specific considerations
Haematological disorders: quinolines may be myelosuppressive.
Psoriasis, psoriatic arthritis: may be more susceptible to severe skin reactions.
G6PD deficiency: observe for haemolytic anaemia.
Porphyria: may exacerbate.
Myasthenia gravis: chloroquine may exacerbate symptoms.
Pregnancy: May cause neurological changes in fetus; ADEC category D.
Lactation: Avoid use; risk of toxicity in the infant.

Adverse effects
Common: nausea, diarrhoea, anorexia, abdominal cramps, rash, alopecia.
Infrequent: vomiting, muscle weakness, vertigo, tinnitus, nerve deafness, headache, nervousness.
Rare: retinopathy, corneal changes, agranulocytosis, aplastic anaemia, thrombocytopenia, bleaching of hair, seizures, erythema multiforme, Stevens–Johnson syndrome, cardiomyopathy, hepatitis, photosensitivity.

Dosage
Where daily dosage is >200 mg, give in divided doses.
Rheumatoid arthritis: 400–600 mg daily for 1–3 months; if desired response is achieved, reduce to 200–400 mg daily. Maximum 6 mg/kg daily based on ideal bodyweight.
Juvenile rheumatoid arthritis, juvenile systemic lupus erythematosus: 5 mg/kg daily.
Discoid and systemic lupus erythematosus: 400–800 mg daily for several weeks. Maintenance, 200–400 mg daily.
Malaria prophylaxis: Start a week before entering, and continue for 4 weeks after leaving, an endemic area. Adult, 400 mg once each week. Child, 6.5 mg/kg (maximum 400 mg) once each week.
Malaria treatment: Adult, 800 mg, then 400 mg after 6–8 hours, then 400 mg daily for 2 days (total dose 2 g). To eliminate liver forms of P. vivax and P. ovale, follow with primaquine. Child, 13 mg/kg (maximum 800 mg), then 6.5 mg/kg after 6 hours, then 6.5 mg/kg daily for 2 days.

Patient counselling
Tell your doctor immediately if you have any difficulty with your sight, particularly in seeing entire words or faces, reduced vision at night or intolerance of bright light. Wear sunglasses when in bright sunlight; it may reduce the chances of eye problems.

Practice points
• benefit may not be seen until after approximately 2–6 months of treatment
• cumulative doses >800 g, age >70 years and daily doses >6 mg/kg (especially in people with hepatic or renal impairment), are risk factors for retinal toxicity; monitor visual function more frequently, eg every 3–6 months
• use hydroxychloroquine in preference to chloroquine in musculoskeletal disorders as it has a lower incidence of ocular toxicity, eg retinopathy
• quinolines are considered less effective, but are better tolerated and less toxic, than other specific antirheumatic drugs; hydroxychloroquine is a reasonable first choice for mild rheumatoid arthritis
• before starting treatment, ask about visual impairment (baseline ophthalmic examination is recommended for patients >40 years, and for those with a personal or family history of eye disease)
• record near visual acuity; assess visual acuity, fundi and visual fields once a year; perform a thorough ophthalmological review after 2 years, then annually
• stop the drug if any adverse ocular changes are found.

Products
HYDROXYCHLOROQUINE TABS 200 MG (AS SULFATE) (ADVAQUENIL®)

10.02.04 OTHER DRUGS FOR RHEUMATOID ARTHRITIS

INFLIXIMAB
Mode of action
Humanised murine monoclonal antibody against tumour necrosis factor (TNF) alfa, preventing inflammatory cell actions in chronic inflammatory diseases.

Indications
Rheumatoid arthritis, with methotrexate treatment.
Ankylosing spondylitis.
Moderate-to-severe refractory Crohn's disease.
Draining enterocutaneous fistula in Crohn's disease.

**Contraindications**
- Serious allergic reaction to infliximab.
- Treatment with anakinra.
- Serious infection, eg sepsis, abscess, active tuberculosis, hepatitis B.

**Specific considerations**
- Latent tuberculosis: infliximab may reactivate disease; check for its presence and, if appropriate, begin treating latent disease before starting infliximab.
- Heart failure: may worsen and increase mortality.
- Antibodies against double stranded DNA (eg lupus): exacerbation or induction of lupus-like syndrome with relative lack of TNF alfa.
- Multiple sclerosis: increases number of cerebral lesions.
- Pregnancy: Limited data; effective contraception is recommended before, during and for 6 months after, treatment; ADEC category C.
- Lactation: No data; do not breastfeed during or for 6 months after treatment.

**Adverse effects**
- More common with higher doses.
- Common: nausea, abdominal pain, vomiting, fever, cough, viral infection, rash, itch, fatigue, vertigo, dizziness, headache, flushing, serum sickness-like reaction, hypersensitivity.
- Infrequent: lupus-like syndrome, development of antinuclear antibodies, anaphylaxis, worsening heart failure, anaemia, leucopenia, thrombocytopenia, pancytopenia, depression, agitation, back pain, myalgia, arthralgia, bacterial infection.
- Rare: aseptic meningitis, demyelination, pleural effusion, interstitial pneumonitis, systemic and cutaneous vasculitis.

**Infusion-related effects**
- More common with first infusion and in people who develop antibodies to infliximab; headache, vertigo, flushing, GI effects, fatigue, fever, chills, urticaria, itch, chest pain or dyspnoea; may be relieved by slowing or temporarily interrupting the infusion.

**Dosage**
- Rheumatoid arthritis: Adult, IV, 3 mg/kg, repeat at 2 and 6 weeks, then every 8 weeks.
- Ankylosing spondylitis: Adult, IV, 5 mg/kg, repeat at 2 and 6 weeks, then every 6 weeks.
- Moderate-to-severe Crohn's disease: Adult, IV, 5 mg/kg, repeat at 2 and 6 weeks, then every 8 weeks. Consider increasing the dose to 10 mg/kg if response is inadequate.
- Enterocutaneous fistulae, adult, IV, 5 mg/kg, repeat at 2 and 6 weeks. If no response after these 3 doses stop infliximab treatment.

**Administration instructions**
- Dilute required dose in 250 mL sodium chloride 0.9%; infuse through a low–protein-binding filter over 2 hours.

**Patient counselling**
- Tell your doctor immediately if you have any signs of allergy (eg shortness of breath, chest tightness) or infection.

**Practice points**
- patients requiring infliximab are usually taking other immunosuppressants, which reduces the frequency of infusion reactions but adds to the degree of immunosuppression
- pretreatment (e.g. antihistamine, paracetamol, corticosteroid) may be used in an attempt to reduce severity of hypersensitivity reaction
- monitor for opportunistic infections during treatment and for up to 6 months after it has stopped because of its long half-life
- monitor cardiac function and stop drug if signs of heart failure occur or worsen.

**Rheumatoid arthritis**
- reserve for disease refractory to treatment with methotrexate
- disease activity increases within weeks of the last dose.

**Crohn's disease**
- risk of delayed hypersensitivity may be high after a break in treatment of >16 weeks; administration after a break of this length is not recommended by the manufacturer
Products
INFLIXIMAB VIAL 100 MG/VIAL (REMICADE®)

10.03. DRUGS FOR GOUT

GOUT
Rationale for drug use
Acute gout: provide symptom relief.
Chronic gout: prevent acute attacks, joint destruction, disability, nephrolithiasis and renal disease, and resolve tophi.

Before starting treatment
Acute gout: Consider diagnosis and exclude infective cause, especially for acute monoarthritis (septic and crystal arthritis may occur together).
Minimize exacerbating factors, eg obesity, alcohol consumption and diuretic use, particularly in tophaceous gout.

Long term treatment: Consider the need for urate-lowering treatment or prophylaxis cautiously. Many patients will not have recurrent acute gout, and long term treatment exposes them to the risk of drug toxicity, which may be severe.

When to start treatment
Asymptomatic hyperuricaemia: Treatment is not indicated.
Acute gout: Treat early to limit morbidity and possibly shorten the duration of attack. Diagnosis may be confirmed by arthrocentesis before or after starting treatment with an NSAID or, less often, colchicine.

Urate-lowering treatment (allopurinol, probenecid)
Indicated in tophaceous gout, urate nephrolithiasis and nephropathy. It may be used in non-tophaceous gout if acute attacks are frequent.
Ensure acute attack is resolved before starting urate-lowering treatment, as changes in plasma uric acid concentration may exacerbate and prolong acute attacks. Consider prophylaxis, with colchicine or NSAID, for the first few months of treatment.

Prophylaxis (colchicine, NSAID)
Consider if acute attacks occur despite adequate urate-lowering treatment, or when urate-lowering treatment is not tolerated or is only partially effective.
Prophylaxis with low dose colchicine or an NSAID is often used when starting urate-lowering treatment to reduce risk of an acute attack.

Drug choice
Acute gout: NSAIDs: treatment of choice for acute gout if not contraindicated. All NSAIDs appear to be equally effective. Use full dose and continue treatment for a week after acute attack has settled.
Corticosteroids: often the preferred treatment for acute gout in patients with complex medical problems where NSAIDs are contraindicated. They may be given systemically (orally or IV), or by intra-articular injection when 1 or 2 joints are involved.
Colchicine: is reserved for acute gout when NSAIDs and corticosteroids (systemic or intra-articular) are contraindicated or inappropriate.

Long term treatment
Urate-lowering treatment
Start with a low dose and increase slowly to minimize risk of precipitating acute gout.
Allopurinol: lowers plasma urate by inhibiting its production; it is commonly used in long term treatment of gout.
Probenecid: reduces plasma urate by increasing renal excretion of uric acid; it is infrequently used for long term treatment of gout. Sometimes specialists use it with allopurinol for tophaceous disease when allopurinol alone is inadequate. Mild renal impairment reduces its effectiveness.
Prophylaxis: Prophylaxis with low dose colchicine or NSAID does not reduce plasma urate concentration or prevent joint damage, and does not take the place of urate-lowering treatment in tophaceous gout. It may be used to prevent acute gout associated with the start of urate-lowering treatment (affects about 25% of patients).
Colchicine—in low doses, it is the preferred agent for long term prophylaxis because of the risk of adverse effects with long term NSAIDs.
NSAIDs: low doses may be used in long term prophylaxis of acute gout.

Factors influencing drug selection
Renal impairment: Gout is common in renal impairment, due to reduced clearance of uric acid. Renal impairment also has consequences for many drugs used for gout:

- corticosteroids are preferred for acute gout
- NSAIDs may worsen renal function and are associated with an increased risk of GI toxicity; avoid use
- allopurinol has a renally excreted active metabolite; reduce dose to avoid toxicity
- probenecid is ineffective if glomerular filtration rate <40 mL/minute
- elimination of colchicine is reduced; may cause myelosuppression; avoid colchicine or reduce dose.

Anticoagulant treatment
Systemic corticosteroids are often the treatment of choice in anticoagulated patients with acute gout. Colchicine can be used; avoid NSAIDs due to risk of GI bleeding. Intra-articular corticosteroids are generally not recommended, seek specialist advice.

Practice points
- although gout is more likely in people with hyperuricaemia:
  - some people with gout have normal urate concentrations
  - many people with hyperuricaemia never develop gout
- instruct patients with recurrent acute attacks to self-treat with NSAID or colchicine at the earliest signs of an attack (most attacks resolve within 7–10 days)
- there is a delay before colchicine’s onset of effect in an acute attack; advise use of an analgesic, eg paracetamol, during this time
- avoid aspirin in analgesic doses as it may increase plasma urate and precipitate acute gout; do not stop low dose aspirin in coronary or cerebrovascular disease.

ALLOPURINOL

Mode of action
Reduces uric acid production by inhibiting xanthine oxidase, and lowers plasma and urinary urate concentrations. Allopurinol is metabolised to oxypurinol, which also inhibits xanthine oxidase.

Indications
Urate-lowering treatment for tophaceous gout.
Long term control of non-tophaceous gout.
Urate nephrolithiasis or acute uric acid nephropathy.
Hyperuricaemia secondary to disease, chemotherapy or radiotherapy.

Contraindications
Allergy to allopurinol.
Starting during acute attack of gout.
Haemochromatosis.

Specific considerations
Renal impairment: Reduce dose; increases risk of adverse effects due to accumulation of oxypurinol.
Pregnancy: Insufficient data available; contact specialized information service; ADEC category B2.
Lactation: Allopurinol and oxypurinol are excreted in breast milk, but no adverse effects have been reported in breastfed infants; contact specialized information service.

Adverse effects
Common: maculopapular or itchy rash.
Infrequent: nausea, vomiting, taste disturbance, diarrhoea, abdominal pain, headache, drowsiness, vertigo, arthralgia.
Rare: allergic reactions, hepatotoxicity, exfoliative dermatitis, nephrolithiasis, acute tubular necrosis, vasculitis, fever, lymphadenopathy, aplastic anaemia, eosinophilia, leucopenia, neutropenia, thrombocytopenia, peripheral neuropathy, cataract (treatment >3 years).

Dosage
Adult: Initially 100 mg once daily, increase by 100 mg daily each month according to response. Usual maintenance, 100–300 mg daily.
Renal impairment: Moderate impairment, 100 mg daily. Severe impairment, 100 mg on alternate days.
Hyperuricaemia associated with cytotoxic treatment: Adult, 600–800 mg daily for 2–3 days before cytotoxic treatment.
Maintenance, reduce dose according to response. Child: 10–20 mg/kg in 1 or 2 doses daily, up to 600 mg daily.

Patient counselling
If you develop a rash, swollen lips or mouth, persistent fever or sore throat, stop taking allopurinol and tell your doctor as soon as possible.
Make sure that you drink lots of fluids during treatment to prevent kidney stones.

Practice points
- wait until attack has settled before starting treatment with allopurinol; changes in uric acid concentration may exacerbate and prolong acute attacks
- continue allopurinol if an acute attack of gout occurs
- Prophylaxis with colchicine or a low dose NSAID may be needed during induction phase with allopurinol (1–3 months)
- check uric acid concentration after 4 weeks and adjust dose; aim for uric acid concentration <0.38 mmol/L
- failure to achieve normal uric acid concentrations may indicate poor compliance
- once treatment is established, continue at the current dose, even during acute attacks of gout
- stop allopurinol if rash develops, there are other signs of allergy, liver function is abnormal, or blood dyscrasias occur
- desensitisation may be possible if allergy occurs and alternative treatment is not appropriate, seek specialist advice
- allopurinol is not indicated for the treatment of asymptomatic hyperuricaemia.

Products
ALLOPURINOL TABS 100 MG (PURINOL®, ZANURIC®, ZYLORIC®)
ALLOPURINOL TABS 300 MG (PURINOL®, ZANURIC®, ZYLORIC®)

COLCHICINE
Mode of action
Inhibits neutrophil migration, chemotaxis, adhesion and phagocytosis in the inflamed area; reduces the inflammatory reaction to urate crystals but has no effect on uric acid production or excretion.

Indications
Marketed: Relief of pain in acute gout.
Accepted: Prophylaxis of recurrent attacks of gout, Prophylaxis of gout when starting urate-lowering treatment.

Contraindications
Previous allergic reaction to colchicine.
History of blood dyscrasias.

Specific considerations
Severe GI disease: may exacerbate symptoms.
Corneal wounds or ulcers: may delay or prevent healing.
Renal impairment: Reduces elimination of colchicine; increases risk of adverse effects. Manufacturer recommends halving the dose in patients with creatinine clearance <50 mL/minute and contraindicates use in severe impairment.
Hepatic impairment: Reduces elimination of colchicine; increases risk of adverse effects. Manufacturer contraindicates use in severe impairment.

Pregnancy: Avoid use; limited data available; ADEC category B2.
Lactation: Avoid use.

Adverse effects
Common: diarrhoea, nausea, abdominal discomfort, vomiting.
Infrequent: GI haemorrhage, rash.
Rare: peripheral neuropathy, myopathy, alopecia, myelosuppression, agranulocytosis, thrombocytopenia, leucopenia, hepatitis, aplastic anaemia, arrhythmias, respiratory failure, hypersensitivity, angioedema.

Dosage
Acute gout: 1 mg initially, followed by 500 micrograms every 2–3 hours until pain relief is obtained or signs of toxicity occur (eg nausea, vomiting, diarrhoea). Maximum total dose is 6 mg. Do not repeat the course within 3 days.
Prophylaxis of gout: 500 micrograms once or twice daily.
Renal impairment: Halve dose if creatinine clearance is <50 mL/minute.

Patient counselling
Nausea, vomiting and diarrhoea often occur within 24 hours of starting colchicine for acute gout; stop treatment immediately when they occur. Do not take >12 tablets (6 mg) in a course to treat acute gout or repeat the course within 3 days.

Practice points
- consider for acute gout when NSAIDs and corticosteroids (systemic or intra-articular) are contraindicated or inappropriate
• in the treatment of acute gout, colchicine toxicity (eg nausea, vomiting, diarrhoea) often occurs within 24 hours, before pain relief is obtained
• joint inflammation subsides gradually within 48 hours in 75–80% of those treated
• measure complete blood count before using colchicine for prophylaxis; repeat at intervals during treatment (after 1 and 6 months then annually)
• after stopping, colchicine is eliminated slowly from the body (can take >10 days); risk of toxicity due to accumulation if acute course repeated too quickly or if drug continued when GI effects occur
• colchicine may be used instead of NSAIDs in patients with heart failure as it does not cause fluid retention.

Products
COLCHICINE TABS 1 MG (COLCHICINE®)

10.04. DRUGS USED IN NEUROMUSCULAR DISORDERS
10.04.01 SKELETAL MUSCLE RELAXANTS

BACLOFEN
Mode of action
Muscle relaxant; it is a structural analogue of gamma-aminobutyric acid (GABA); GABAB agonist. Inhibits transmission at spinal level and depresses the CNS.

Indications
Chronic spasticity associated with multiple sclerosis and spinal cord lesions.
Chronic spasticity of cerebral origin (intrathecal use, seek specialist advice).

Contraindications
Peptic ulcer.

Specific considerations
Psychiatric disorders, cerebrovascular disease, epilepsy, Parkinson's disease, respiratory disease, hypertonic bladder sphincter: risk of aggravation.
Diabetes: risk of increased blood glucose concentration.
Porphyria: risk of acute attack.
Renal impairment: Avoid use in severe impairment; may require dose reduction in mild-to-moderate impairment.
Hepatic impairment: Use with caution; increased risk of adverse effects; monitor liver function.
Pregnancy: Limited data available; ADEC category B3.
Lactation: Can be used; may inhibit lactation.

Adverse effects
Common: nausea, vomiting, constipation, diarrhoea, rash, hypotension, respiratory depression, muscular weakness, myalgia, drowsiness, dizziness, ataxia, headache, seizures, insomnia, confusion, euphoria, depression, hallucinations, tremor, nystagmus, tinnitus, visual disturbances, urinary disorders (enuresis, urinary retention).
Infrequent or rare: paraesthesia, dyskinesia, paradoxical increase in spasticity, arrhythmia, dyspnoea, altered liver function tests.
Withdrawal syndrome: Sudden withdrawal of baclofen may be followed by anxiety, altered mental status, seizures (including status epilepticus), high fever and rebound spasticity.
Progression to rhabdomyolysis, multiple organ failure and death has been reported following abrupt interruption of intrathecal baclofen.

Dosage
Adult: Oral, initially 5 mg 3 times daily, increase gradually by 15 mg daily every fourth day until therapeutic effect is obtained. Usual range, 10–25 mg 3 times daily. Doses up to 120–150 mg daily may be given in hospitalised people.
Elderly: Oral, initially 5–10 mg daily, increase by smaller increments and at longer intervals.
Child: Oral, initially 0.75 mg/kg daily in 3–4 divided doses, increase gradually at 3-day intervals to 2 mg/kg daily in 3–4 divided doses.

Administration instructions
Take with food to minimize GI adverse effects.

Patient counselling
Avoid drinking alcohol as it may worsen some of the side effects of baclofen.

Practice points
• adverse effects usually occur at the start of treatment and can be minimized by beginning at low dose and increasing dosage gradually
• withdraw treatment if no benefit is apparent within 6–8 weeks; reduce dosage gradually over about 2 weeks to prevent a withdrawal syndrome
• intrathecal administration may be tried in people who fail to respond to oral administration or cannot tolerate high doses orally
• carefully program and monitor the intrathecal infusion system to prevent administration accidentally stopping as withdrawal syndrome may result.

Products
BACLOFEN AMPS 10 MG/AMP 20 ML AMP (NOT REGISTERED)
BACLOFEN TABS 10 MG (LIORESAL®)

DANTROLENE

Mode of action
A direct acting skeletal muscle relaxant. Decreases muscle contraction by interfering with calcium release from sarcoplasmic reticulum.

Indications
Chronic spasticity associated with spinal cord injury, head injury, multiple sclerosis, cerebral palsy or stroke (oral) Malignant hyperthermia (IV).

Contraindications
Active hepatic disease (eg hepatitis, cirrhosis).

Specific considerations
History of hepatic disease: increased risk of hepatotoxicity. Impaired cardiac or pulmonary function: increased risk of exacerbation. Treatment with oestrogens: may increase risk of hepatotoxicity in women >35 years; use combination cautiously. Renal impairment: May require dose reduction. Children: Safety not established in children <5 years. Pregnancy: Limited data available; ADEC category B2. Lactation: No data available; avoid use.

Adverse effects
drowsiness, dizziness, fatigue, diarrhoea, nausea, vomiting, anorexia, constipation, elevated hepatic enzymes, hepatitis (dose-related), rash, unstable BP, tachycardia, dyspnoea, cardiac failure, enuresis, urinary retention, headache, insomnia, nervousness, confusion, depression, visual disturbances, aplastic anaemia, leucopenia, lymphocytic lymphoma, seizures, pleural effusion with pericarditis (IV).

Dosage
Chronic spasticity
Adult, oral, initially 25 mg once daily, increase to 25 mg 2–4 times daily, and then by 25 mg increments up to 50 mg 2–4 times daily according to response. Maximum, 400 mg daily.
Child, oral, initially 0.5 mg/kg twice daily, increased to 0.5 mg/kg 3–4 times daily, and then by increments up to 2 mg/kg 3 times daily according to response. Maximum, 200 mg daily.
Malignant hyperthermia: IV, initially 1 mg/kg repeated every 1–2 minutes until symptoms subside, or to a maximum cumulative dose of 10 mg/kg.

Practice points
Chronic spasticity
• stop treatment if no benefit is apparent within 4–6 weeks
• adverse effects usually occur at start of treatment and can be minimized by beginning treatment at a low dose and increasing dosage gradually
• stop treatment if diarrhoea is severe; if it recurs upon readministration, stop treatment permanently
• monitor liver function at the beginning of treatment and at intervals of 1–2 months; stop treatment if there are persistent abnormalities in liver function tests.

Products
DANTROLENE CAPS 25 MG (AS SODIUM) (NOT REGISTERED)
DANTROLENE CAPS 100 MG (AS SODIUM) (NOT REGISTERED)
**TIZANIDINE**

**Mode of action**
Tizanidine hydrochloride is a centrally acting skeletal muscle relaxant. It is an α2-adrenergic agonist structurally related to clonidine and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurones.

**Indications**
Spasticity associated with multiple sclerosis or spinal cord injury or disease.

**Drug interactions**
The CNS effects of tizanidine may be enhanced by alcohol or other CNS depressants. There may be an additive hypotensive effect when tizanidine is used in patients receiving antihypertensive therapy; bradycardia may also be enhanced if given with beta blockers or digoxin. Caution should be exercised when tizanidine is given with drugs known to increase the QT interval. The clearance of tizanidine has been reported to be lower in women receiving hormonal contraceptives.

**Contraindications**
severe hepatic impairment.

**Specific considerations**
- Elderly, renal impairment: decrease the dose.
- Pregnancy: use only if potential benefit outweighs risk.
- Breast feeding: use only if potential benefit outweighs risk.
- Monitor liver function monthly for first 4 months and in those who develop unexplained nausea, anorexia or fatigue.
- Drowsiness may affect performance of skilled tasks (e.g. driving).

**Adverse effects**
Common: Drowsiness, fatigue, dizziness, dry mouth, nausea, gastrointestinal disturbances, hypotension.
Infrequent: bradycardia, insomnia, hallucinations, and altered liver enzymes.
Rare: acute hepatitis.

**Dosage**
The usual initial daily dose in the UK in the management of spasticity is the equivalent of 2 mg of the base given as a single dose. The dose may be increased thereafter according to response in steps of 2 mg at intervals of at least 3 to 4 days, usually up to 24 mg daily given in 3 or 4 divided doses. A similar schedule, with an initial daily dose of 4 mg, increased as required in steps of 2 to 4 mg, is used in the USA. The maximum recommended dose is 36 mg daily.

**Products**
- **TIZANIDINE TABS 2 MG (AS HCL) (SIRDALUD®)**
- **TIZANIDINE TABS 4 MG (AS HCL) (SIRDALUD®)**
<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (hours)</th>
<th>Number of doses/day</th>
<th>Routes</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>aspirin</td>
<td>0.25 (2–19)1</td>
<td>3–4</td>
<td>oral</td>
<td>nonselective; analgesic and antiplatelet agent (inhibits platelet COX for life of platelet unlike other nonselective NSAIDs); available without prescription</td>
</tr>
<tr>
<td>celecoxib</td>
<td>4–15</td>
<td>1–2</td>
<td>oral</td>
<td>selective COX-2 inhibitor; high doses associated with increased risk of cardiovascular events; TGA has issued a warning</td>
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<td>diclofenac</td>
<td>1–2</td>
<td>2–3</td>
<td>oral, rectal, topical</td>
<td>nonselective; available without prescription</td>
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<td>5–20</td>
<td>2</td>
<td>oral</td>
<td>nonselective</td>
</tr>
<tr>
<td>ibuprofen</td>
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<td>3–4</td>
<td>oral, topical</td>
<td>nonselective; available without prescription</td>
</tr>
<tr>
<td>indomethacin</td>
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<td>2–4</td>
<td>oral, rectal oral, topical</td>
<td>nonselective</td>
</tr>
<tr>
<td>ketoprofen</td>
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<td>12</td>
<td>oral, rectal, topical</td>
<td>nonselective</td>
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<tr>
<td>ketorolac</td>
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<td>IM, IV, oral</td>
<td>nonselective</td>
</tr>
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<td>mefenamic acid</td>
<td>3–4</td>
<td>3</td>
<td>oral</td>
<td>nonselective</td>
</tr>
<tr>
<td>meloxicam</td>
<td>20</td>
<td>1</td>
<td>oral</td>
<td>selective COX-2 inhibitor (at low dosage)</td>
</tr>
<tr>
<td>naproxen</td>
<td>12–15</td>
<td>2 (1)2</td>
<td>oral</td>
<td>nonselective; available without prescription</td>
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<tr>
<td>parecoxib</td>
<td>3.5–4 (6.5–7)1</td>
<td>1 (single peri-operative dose)</td>
<td>IM, IV</td>
<td>selective COX-2 inhibitor; TGA proposes to cancel its registration due to safety concerns</td>
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<tr>
<td>piroxicam</td>
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<td>1</td>
<td>oral, topical</td>
<td>nonselective</td>
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<td>1–2</td>
<td>oral</td>
<td>nonselective</td>
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<td>2–3</td>
<td>2–3</td>
<td>oral</td>
<td>nonselective</td>
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</tbody>
</table>

1active metabolite  
2controlled release forms
CHAPTER 11 EYE

11.01 ANTI-INFECTIVE EYE PREPARATIONS

11.01.01 AMINOGLYCOSIDES

GENTAMYCIN (EYE)

Indications
Marketed: Infections of the eye and surrounding structures caused by susceptible bacteria
Accepted: Prophylaxis after surgery

Specific considerations
Pregnancy: Safe to use.
Lactation: Safe to use.

Adverse effects
Common: ocular irritation, superficial punctate keratitis
Other: delayed corneal epithelial wound healing, potential retinal toxicity (if there is leakage through corneoscleral wound)

Dosage
Bacterial conjunctivitis, 1 drop every 2–4 hours for 2 days; then if there is improvement, 1 drop 4 times daily for 5 days.
Prevention of infection (after superficial trauma or surgery), 1 drop 4 times daily until epithelium healed (rarely >4 days).

Patient counselling
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Practice points
- gentamicin should be reserved for use by ophthalmologists and for serious infections not responding to treatment with other topical antibacterials (after taking sample for microbiological culture)

Products
GENTAMYCIN EYE (EAR) DROPS 0.3 % (AS SULFATE) 10 ML BOTTLE (APIGEN®, COLIRCUSI GENTAMYCIN®, GENTADAR®)
GENTAMYCIN EYE OINTMENT 0.3 % (AS SULFATE) 5 GM TUBE (APIGEN®, OFTALMOSA®, OPHTAGRAM®)
GENTAMYCIN MINIMS 0.3 % (AS SULFATE) 0.5 ML MINIMS (MINIMS GENTAMYCIN SULPH®)

NEOMYCIN (EYE)

Indications:
Infections of the eye and surrounding structures caused by susceptible bacteria
Marketed: Infections of the eye caused by susceptible bacteria
Accepted: Prophylaxis after eye surgery (gentamicin or tobramycin)

Specific considerations
Pregnancy: Safe to use.
Lactation: Safe to use.

Adverse effects
Common: ocular irritation, superficial punctate keratitis
Other: delayed corneal epithelial wound healing, potential retinal toxicity (if there is leakage through corneoscleral wound)

Dosage
Bacterial conjunctivitis, 1 drop every 2–4 hours for 2 days; then if there is improvement, 1 drop 4 times daily for 5 days.

Patient counselling
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Practice points
- preservative-free and relatively expensive preparation; reserve for more difficult conditions (eg MRSA infective keratitis with benzalkonium allergy)
Products
NEOMYCIN EYE DROPS 3.5 MG/ML (AS SULFATE)  10 ML BOTTLE (OPHTAMYCIN®)

TOBRAMYCIN (EYE)
Indications
Marketed: Infections of the eye and surrounding structures caused by susceptible bacteria
Accepted: Prophylaxis after surgery
Specific considerations
Pregnancy: Safe to use.
Lactation: Safe to use.
Adverse effects
Common: ocular irritation, superficial punctate keratitis
Other: delayed corneal epithelial wound healing, potential retinal toxicity (if there is leakage through corneoscleral wound)
Dosage
Bacterial conjunctivitis
1 drop every 2–4 hours for 2 days; then if there is improvement, 1 drop 4 times daily for 5 days.
Ointment may be used as an adjunct to drops at night, or as a single agent 3 times daily, eg in children.
Prevention of infection (after superficial trauma or surgery): 1 drop 4 times daily until epithelium healed (rarely >4 days).
Patient counselling
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.
Practice points
- tobramycin should be reserved for use by ophthalmologists and for serious infections not responding to treatment with other topical antibacterials (after taking sample for microbiological culture)

Products
TOBRAMYCIN 0.3 % + DEXAMETHASONE 0.1 % EYE DROPS  5 ML BOTTLE (TOBRADEX®)
TOBRAMYCIN 0.3 % + DEXAMETHASONE 0.1 % EYE OINTMENT  3.5 GM (TOBRADEX®)
TOBRAMYCIN EYE DROPS 0.3 %  5 ML BOTTLE (IKOBEL®, TOBRACIN®, TOBREX®, TOBRASTILL®)
TOBRAMYCIN EYE OINTMENT 0.3 %  3.5 GM TUBE (TOBREX®)

11.01.02 QUINOLONES (EYE)

CIPROFLOXACIN (EYE)
Mode of action
Bactericidal.
Indications
Keratitis and severe conjunctivitis caused by susceptible bacteria
Eye infections caused by susceptible bacteria, eg bacterial keratitis
Specific considerations
Pregnancy: Avoid use (alternatives preferred as limited data available); ADEC category B3.
Lactation: Suitable if necessary.
Adverse effects
Common: mild transient ocular irritation, lid margin crusting and scaling, unpleasant taste
Infrequent: keratitis (photophobia, corneal infiltrates and staining), allergic reactions
Corneal perforation: A recent retrospective medical record review of cases of bacterial keratitis found the rate of corneal perforation was 14% with topical ofloxacin compared to 1% with fortified antibiotics (hospital prepared cefazolin 5% and tobramycin 1.36% eye drops).
Dosage
Severe bacterial conjunctivitis: 1 drop every 2–4 hours for 2 days; then if there is improvement, 1 drop 4 times daily for 5 days.
Keratitis: 1 drop every 5 minutes for the first hour, then once every hour until there is improvement; decrease frequency according to clinical response (only under supervision of ophthalmologist).
Patient counselling
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- other antibacterials are preferred for conjunctivitis, to slow emerging resistance
- reserve for ophthalmologist use, especially when used for bacterial keratitis
- excellent gram-negative activity and good gram-positive activity

**Products**

**CIPROFLOXACIN EYE DROPS 0.3 % (AS HCL) 5-10 ML BOTTLE (CILOXAN®, CIPROCIN®, FLOXIN®)**

**LOMEFLOXACIN**

**Adverse Effects and Precautions**
As for Ciprofloxacin,

**Uses and Administration**
Loefloxacin eye drops is used topically as the hydrochloride as 0.3% eye drops for the treatment of bacterial conjunctivitis and as 0.3% ear drops for the treatment of otitis externa and otitis media.

**Practice points**
Streptococcus pneumoniae is relatively resistant to lomefloxacin

**Products**

**LOMEFLOXACIN EYE DROPS 3 MG/ML (AS HYDROCHLORIDE) 5 ML BOTTLE (OKACIN®)**

**OFLOXACIN (EYE)**

**Mode of action**
Bactericidal.

**Indications**
Marketed: Severe conjunctivitis caused by susceptible bacteria
Accepted: Keratitis caused by susceptible bacteria

**Specific considerations**
Pregnancy: Avoid use (alternatives preferred as limited data available); ADEC category B3.
Lactation: Suitable if necessary.

**Adverse effects**
Common: mild transient ocular irritation, lid margin crusting and scaling, unpleasant taste
Infrequent: keratitis (photophobia, corneal infiltrates and staining), allergic reactions
Corneal perforation: A recent retrospective medical record review of cases of bacterial keratitis found the rate of corneal perforation was 14% with topical ofloxacin compared to 1% with fortified antibiotics (hospital prepared cefazolin 5% and tobramycin 1.36% eye drops).

**Dosage**
Severe bacterial conjunctivitis: 1 drop every 2–4 hours for 2 days; then if there is improvement, 1 drop 4 times daily for 5 days.
Keratitis: 1 drop every 5 minutes for the first hour, then once every hour until there is improvement; decrease frequency according to clinical response (only under supervision of ophthalmologist).

**Patient counselling**
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- reserve for ophthalmologist use, especially when used for bacterial keratitis
- other antibacterials are preferred for conjunctivitis, to slow emerging resistance

**Products**

**OFLOXACIN EYE DROPS 0.3 % (OFLOX®, OPTIFLOX®)**

**11.01.03 OTHER ANTIBACTERIALS**

**CHLORAMPHENICOL (EYE)**

**Indications**
Marketed: Infections of the eye and lids due to susceptible organisms
Accepted: Prophylaxis after surgery or superficial trauma

**Contraindications**
Allergy to chloramphenicol

**Specific considerations**
- Pregnancy: Safe to use; ADEC category A.
- Lactation: Safe to use.

**Adverse effects**
- Infrequent: unpleasant taste
- Rare: allergy, eg local reactions, angioedema, anaphylaxis, dermatitis (often moderately severe)

**Dosage**
- Bacterial blepharitis: Massage ointment into lid margin 2–3 times daily.
- Bacterial conjunctivitis: 1 drop every 2–4 hours for 2 days; then if there is improvement, 1 drop 4 times daily for 5 days. Ointment may be used as an adjunct to drops at night, or as a single agent 3 times daily, eg in children.
- Prevention of infection (after superficial trauma or surgery): 1 drop 4 times daily until epithelium healed (rarely >4 days).

**Patient counselling**
- If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- large population based studies have found no association between use of chloramphenicol eye drops and aplastic anaemia
- broad spectrum bacteriostatic activity against Gram-positive, Gram-negative (except Pseudomonas spp.) and anaerobic bacteria; good ocular penetration

**Products**
- CHLORAMPHENICOL 0.5 % + DEXAMETHASONE 1 % (AS SODIUM PHOSPHATE) EYE DROPS 5 ML BOTTLE (SPERSADEX COMP®, PHENIDEX®)
- CHLORAMPHENICOL EYE DROPS 0.5 % 10 ML BOTTLE (CHLORAMPHENICOL®, CHLOROPTIC®, COLIRCUSI CHLORAMPHENICOL®, ISOMEPHENICOL®, PHENICOL®)
- CHLORAMPHENICOL EYE OINTMENT 1 % 4-5 GM TUBE (CHLORAMPHENICOL®, PHENICOL®)
- CHLORAMPHENICOL MINIMS O.5 % 0.5 ML MINIMS (MINIMS CHLORAMPHENICOL®)

**ERYTHROMYCIN (EYE)**

**Indications**
- Infections of the eye or lids caused by susceptible bacteria

**Contraindications**
- Allergy to neomycin, polymyxin or gramicidin

**Specific considerations**
- Ocular atopy—may be exacerbated.
- Pregnancy: Safe to use.
- Lactation: Suitable if necessary.

**Adverse effects**
- Common: contact allergy (neomycin)
- Infrequent: irritation, mild conjunctivitis (polymyxin)
- Rare: contact allergy (polymyxin, gramicidin)

**Dosage**
- Bacterial conjunctivitis: 1 drop every 2–4 hours for 2 days; then if there is improvement, 1 drop 4 times daily for 5 days. Ointment may be used as an adjunct to drops at night, or as a single agent 3 times daily, eg in children.
- Other infections: Initially 1 drop every 15–30 minutes, reducing to 1 drop 2–4 times daily as the infection settles.

**Patient counselling**
- If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- combination of neomycin, polymyxin, bacitracin and gramicidin is active against many Gram-negative organisms (including Pseudomonas spp.) and Gram-positive organisms

**Products**
- ERYTHROMYCIN EYE OINTMENT 0.5 % (EROCIN®, ERYTHROMYCIN®)
**FUSIDIC ACID (EYE)**

**Indications**
Infections of the eye (conjunctivitis) or lids (blepharitis) caused by susceptible bacteria

**Contraindications**
Hypersensitivity to any component

**Adverse effects**
Common: transient stinging
Rare: allergy

**Dosage**
One drop into the eye twice daily

**Products**
FUSIDIC ACID EYE GEL (DROPS) 1% 5 GM TUBE (FUCITHALMIC®, OPTIFUCIN®)

**POLYMYXIN B WITH NEOMYCIN COMBINATIONS**

**Mode of action**
Broad bacteriostatic activity including C. trachomatis.

**Indications**
Superficial ocular infection caused by susceptible organisms

**Contraindications**
Allergy to tetracycline
Photodermatosis

**Specific considerations**
Children: No reports of tooth discoloration at usual topical doses; considered relatively safe, as systemic exposure is very low.
Pregnancy: Unlikely to cause adverse effects at topical doses.
Lactation: Safe to use.

**Adverse effects**
Rare: allergic reaction, photodermatosis

**Dosage**
Bacterial blepharitis: Massage ointment into eyelid margin 2–3 times daily.
Bacterial conjunctivitis: 3 times daily for 1 week.
Trachoma: 3 times daily for 1 month.

**Practice points**
- tetracycline ointment is not necessary for trachoma if adequate systemic treatment is given

**Products**
POLYMYXIN B SULFATE 5,000 IU+NEOMYCIN SULFATE 1,700 IU/ML+DEXAMETHASONE 25 IU EYE DROPS (MAXITROL®)

**11.01.04 ANTVIRALS**

**ACICLOVIR (EYE)**

**Indications**
Marketed: Herpes simplex keratitis
Accepted: Herpes zoster ophthalmicus with corneal involvement

**Specific considerations**
Pregnancy: Safe to use; ADEC category B3.
Lactation: Safe to use.

**Adverse effects**
Common: transient mild stinging after instillation
Infrequent: superficial punctate keratitis, allergic reactions

**Dosage**
Apply about 1 cm of ointment into the lower conjunctival sac 5 times daily for 14 days, or for 3 days after corneal epithelium healed, whichever is shorter.

**Practice points**
- for frequently recurring herpes simplex epithelial keratitis, advise patients to keep a spare tube of ointment and start treatment at the first sign of recurrence
11.02 TREATMENT OF GLAUCOMA
11.02.01 BETA-BLOCKERS (EYE)

**BETAXOLOL (EYE)**

**Mode of action**
Reduce aqueous humour formation, probably by blockade of the beta receptors on the ciliary epithelium.

**Indications**
Glaucoma: All types of glaucoma

**Contraindications**
Reversible airways disease, eg asthma (cardioselective agents, ie betaxolol, may be used with care)
Bradyarrhythmia, second or third degree atrioventricular block
Shock

**Specific considerations**
Potentially the same as for systemic beta-blockers.
Treatment with systemic nonselective beta-blocker—reduces intraocular pressure. Adding topical beta-blocker when taking a systemic beta-blocker offers some additional pressure reduction but may increase systemic adverse effects.
Treatment with verapamil: potential for profound bradycardia; avoid combination.
Surgery: Theoretical increased risk of bradycardia and hypotension during surgery.
Elderly: Systemic adverse effects, eg hypotension (may cause falls), are more common.
Children: May cause apnoea in neonates and bradycardia in children.
Pregnancy: May cause fetal bradycardia; ADEC category C.
Lactation: Unlikely to cause adverse effects at usual doses.

**Adverse effects**
The most important adverse effects are systemic.
Common: stinging on instillation (especially betaxolol solution), bradycardia
Infrequent: decreased corneal sensation, hypotension, syncope, impotence, decreased libido, fatigue, confusion, hallucinations, bronchospasm

**Dosage**
1 drop twice daily.

**Patient counselling**
Immediately after instilling a drop, close eyes and press on the tear duct for 3 minutes to increase the effectiveness of the eye drop.
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- use of suspension may reduce local stinging of betaxolol

**Products**
**BETAXOLOL EYE DROPS 0.5 % (AS HCL) 5-10 ML BOTTLE (BETOPTIC®, APIXOL®)**

**CARTEOLOL**

**Mode of action**
It is a non-cardioselective beta blocker. It is reported to possess intrinsic sympathomimetic activity but lacks significant membrane-stabilising activity.

**Uses and Administration**
Eye drops containing carteolol hydrochloride 1% are instilled twice daily to reduce raised intra-ocular pressure in open-angle glaucoma and ocular hypertension.

**Products**
**CARTEOLOL EYE DROPS 1 % (AS HCL) 3-5 ML BOTTLE (TEOPTIC®, CARTEOL®)**

**TIMOLOL (EYE)**

**Mode of action**
Reduce aqueous humour formation, probably by blockade of the beta receptors on the ciliary epithelium.
Indications
Glaucoma: All types of glaucoma

Contraindications
Reversible airways disease, eg asthma (cardioselective agents, ie betaxolol, may be used with care)
Bradyarrhythmia, second or third degree atrioventricular block
Shock

Specific considerations
Potentially the same as for systemic beta-blockers.
Treatment with systemic nonselective beta-blocker: reduces intraocular pressure. Adding topical beta-blocker when taking a systemic beta-blocker offers some additional pressure reduction but may increase systemic adverse effects.
Treatment with verapamil: potential for profound bradycardia; avoid combination.
Surgery: Theoretical increased risk of bradycardia and hypotension during surgery.
Elderly: Systemic adverse effects, eg hypotension (may cause falls), are more common.
Children: May cause apnoea in neonates and bradycardia in children.
Pregnancy: May cause fetal bradycardia; ADEC category C.
Breastfeeding: Unlikely to cause adverse effects atusual doses.

Adverse effects.
The most important adverse effects are systemic.
Common: stinging on instillation (especially betaxolol solution), bradycardia
Infrequent: decreased corneal sensation, hypotension, syncope, impotence, decreased libido, fatigue, confusion, hallucinations, bronchospasm

Dosage
Conventional drops, 1 drop of 0.5% twice daily.
Infant <12 months: 1 drop of 0.25% once daily.

Patient counselling
- Immediately after instilling a drop, close eyes and press on the tear duct for 3 minutes to increase the effectiveness of the eye drop.
- If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Products
TIMOLOL EYE DROPS 0.5 % (AS MALEATE) (APIMOL®, CUSIMOLOL®, NYOLOL®, OPHTAMOLOL®, TIMOLOL®, TIMOPTOL®)

11.02.02 ALPHA2 AGONISTS (EYE)

BRIMONIDINE (EYE)
Mode of action
Reduce intraocular pressure by suppressing formation and increasing outflow of aqueous humour.

Indications
Chronic open angle glaucoma or ocular hypertension when beta-blockers are not tolerated or are contraindicated
Chronic open angle glaucoma
Prevention of ocular hypertension following laser surgery
Acute closed angle glaucoma (before laser iridotomy)

Specific considerations
Pregnancy: Apraclonidine, avoid use; ADEC category B3.
Brimonidine, suitable if necessary; ADEC category B1.
Lactation: No data available; unlikely to be a concern.

Adverse effects
Common: ocular irritation, ocular allergic reaction, blepharitis, conjunctival blanching, lid retraction, dry mouth and nose, taste disturbance, fatigue, headache, drowsiness, dizziness
Infrequent: systemic allergic reactions, depression, palpitations, systemic hypotension

Dosage
1 drop 2–3 times daily.

Patient counselling
Immediately after instilling a drop, close eyes and press on the tear duct for 3 minutes to increase the effectiveness of the eye drop.
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- drowsiness may affect performance of skilled tasks, eg driving
- may be used by ophthalmologists to prevent ocular hypertension following laser surgery

**Products**
**BRIMONIDINE EYE DROPS 0.2 % (AS TARTARATE) 5 ML BOTTLE (ALPHAGAN®)**

### 11.02.03 CHOLINERGICS (EYE)

**PILOCARPINE (EYE)**

**Mode of action**
Cholinergic effect contracts iris sphincter (miotic) and ciliary muscle, which increases outflow through the trabecular meshwork.

**Indications**
- Chronic open angle glaucoma
- Acute closed angle glaucoma
- Reversal of weak mydriatics (not recommended)
- Chronic open angle glaucoma
- Acute closed angle glaucoma (pilocarpine)

**Contraindications**
- Uveitis (exacerbates blood–ocular barrier breakdown)
- Secondary glaucomas associated with extensive outflow obstruction (ineffective, may worsen)

**Specific considerations**
- Acute primary closed angle glaucoma—concentrations >2% may exacerbate condition.
- Pregnancy: Pilocarpine has been implicated in neonatal hypothermia, restlessness, seizures and diaphoresis.
- Lactation: Safe to use.
- Coexisting conditions: High myopia, aphakia, peripheral retinal degeneration, previous retinal detachment—increased risk of retinal detachment.
- Surgery: Theoretical increased risk of bradycardia and hypotension during surgery.
- Children: Infrequently iris cysts or nodular excrescences of pupillary ruff develop with prolonged use; these rarely affect vision.

**Adverse effects**
Mostly ocular and concentration dependent.
- Common: fluctuating blurred vision, accommodative spasm and frontal headache in people <40 years (usually decreasing after 2–4 weeks; simple analgesics may reduce pain), miosis, ocular irritation, follicular conjunctivitis
- Infrequent: lacrimation, blepharospasm, photophobia
- Rare: retinal detachment, anorexia, nausea, vomiting, diarrhoea, colic, fatigue, bronchospasm, increased bronchial secretions, bradycardia, hypotension

**Dosage**
- Chronic primary open angle glaucoma
  - Initial, 1 drop of 0.5% or 1% 3–4 times daily.
  - Usual, 1 drop of 2% 4 times daily.
  - Maximum, 1 drop of 4% (light iris) or 6% (dark iris) 4 times daily.
- Reversal of mydriasis: 1 drop of 1%.

**Administration instructions**
Instil pilocarpine drops last if multiple drops are prescribed.

**Patient counselling**
Immediately after instilling a drop, close eyes and press on the tear duct for 3 minutes to increase the effectiveness of the eye drop.

If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- minimise adverse effects by starting with the lowest concentration and increasing slowly
- miosis is potentially permanent with long term use and may reduce vision in dim light, worsen the effect of a central visual opacity and constrict the visual field
- warn patients of visual blurring and reassess acuity for driving
Products
PILOCARPINE EYE DROPS 2 %
PILOCARPINE EYE DROPS 4 % (APICARPINE®)
PILOCARPINE MINIMS 2 % 0.5 ML MINIMS (NOT REGISTERED)

11.02.04 PROSTAGLANDIN ANALOGUES (EYE)

BIMATOPROST (EYE)

Mode of action
Reduce intraocular pressure by increasing uveoscleral outflow of aqueous humour.

Indications
Glaucoma

Contraindications
Allergy to the prostaglandin analogue
Active intraocular inflammation (iritis/uveitis)

Specific considerations
Coexisting conditions: Aphakia, pseudophakia, torn posterior lens or capsule, known risk factors for macular oedema: increased risk of developing macular oedema.
History of intraocular inflammation (iritis/uveitis): monitor carefully.

Pregnancy: Avoid use; no data available; ADEC category B3.
Lactation: No data available, but unlikely to be of concern; latanoprost is safe to use.

Adverse effects
Common: ocular itch, superficial punctate keratitis, blepharitis, conjunctival oedema, dry eyes, headache
Infrequent: eyelid oedema, iritis

Common: gradual (over months to years), usually irreversible increase in iris pigmentation in treated eyes, especially those of mixed colour, eg blue/brown; darkening, lengthening and thickening of the eyelashes, conjunctival hyperaemia (usually transient)

Infrequent: reversible macular oedema (including cystic oedema), darkening of palpebral skin

Dosage
1 drop once daily, preferably at night.

Patient counselling
Immediately after instilling a drop, close eyes and press on the tear duct for 3 minutes to increase the effectiveness of the eye drop.
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Practice points
- warn patients, especially those with eyes of mixed colour, of a possible permanent increase in iris pigmentation; heterochromia may result if only one eye is treated
- instil in the evening for optimal effect
- drugs in this class are structurally different; if response to one is poor, consider trying another

Products
BIMATOPROST EYE DROPS 0.03 % 3 ML BOTTLE (LUMIGAN®)

LATANOPROST (EYE)

Mode of action
Reduce intraocular pressure by increasing uveoscleral outflow of aqueous humour.

Indications
Glaucoma

Contraindications
Allergy to the prostaglandin analogue
Active intraocular inflammation (iritis/uveitis)

Specific considerations
History of herpes simplex keratitis: may stimulate recurrence.
Aphakia, pseudophakia, torn posterior lens or capsule, known risk factors for macular oedema: increased risk of developing macular oedema.

Pregnancy: Avoid use; no data available; ADEC category B3.
Lactation: No data available, but unlikely to be of concern; latanoprost is safe to use.

Adverse effects
Common: ocular irritation (preservative benzalkonium chloride), blepharitis, punctate corneal epithelial erosions, bitter taste, rash
Infrequent: anterior uveitis, recurrence of herpes simplex keratitis
Rare: hypertension, asthma
Common: gradual (over months to years), usually irreversible increase in iris pigmentation in treated eyes, especially those of mixed colour, eg blue/brown; darkening, lengthening and thickening of the eyelashes, conjunctival hyperaemia (usually transient)
Infrequent: reversible macular oedema (including cystic oedema), darkening of palpebral skin

Dosage
1 drop once daily, preferably at night.
Combination with timolol 0.5%: 1 drop once daily.

Patient counselling
Immediately after instilling a drop, close eyes and press on the tear duct for 3 minutes to increase the effectiveness of the eye drop.

If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Practice points
- do not use latanoprost 0.005% with timolol 0.5% to start treatment; combination may be appropriate when latanoprost alone is insufficient, however, use each drug separately if twice daily timolol is needed

Products
LATANOPROS 50 MCG/ML + TIMOLOL 5 MG/ML EYE DROPS 2.5 ML BOTTLE (XALACOM®)
LATANOPROST EYE DROPS 50 MCG/ML 2.5 ML BOTTLE (XALATAN®)

TRAVOPROST (EYE)

Mode of action
Reduce intraocular pressure by increasing uveoscleral outflow of aqueous humour.

Indications
Glaucoma

Contraindications
Allergy to the prostaglandin analogue
Active intraocular inflammation (iritis/uveitis)

Specific considerations
Aphakia, pseudophakia, torn posterior lens or capsule, known risk factors for macular oedema: increased risk of developing macular oedema.
History of intraocular inflammation (iritis/uveitis): monitor carefully.
Pregnancy: Avoid use; no data available; ADEC category B3.
Lactation: No data available, but unlikely to be of concern; latanoprost is safe to use.

Adverse effects
Common: itch, keratitis, headache
Infrequent: hypotension, bradycardia, blepharitis, rhinitis
Common: gradual (over months to years), usually irreversible increase in iris pigmentation in treated eyes, especially those of mixed colour, eg blue/brown; darkening, lengthening and thickening of the eyelashes, conjunctival hyperaemia (usually transient)
Infrequent: reversible macular oedema (including cystic oedema), darkening of palpebral skin

Dosage
1 drop once daily, preferably in the evening.

Patient counselling
Immediately after instilling a drop, close eyes and press on the tear duct for 3 minutes to increase the effectiveness of the eye drop.

If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Practice points
- warn patients, especially those with eyes of mixed colour, of a possible permanent increase in iris pigmentation; heterochromia may result if only one eye is treated
- instil in the evening for optimal effect
- drugs in this class are structurally different; if response to one is poor, consider trying another
11.02.05 CARBONIC ANHYDRASE INHIBITORS (EYE)

BRINZOLAMIDE (EYE)

**Mode of action**
Inhibit carbonic anhydrase II (predominant subtype found in the eye) and reduce elevated intraocular pressure.

**Indications**
- Glaucoma
- Ocular hypertension
- Open angle glaucoma

**Contraindications**
- Sulfonamide allergy

**Specific considerations**
- Corneal grafts, endothelial dystrophy: may cause corneal oedema and precipitate corneal decompensation.
- Pregnancy: Avoid use; no human data available; ADEC category B3.
- Lactation: No human data available.

**Adverse effects**
- Common: blurred vision
- Infrequent: conjunctivitis, lid margin crusting, keratitis, photophobia
- Common: ocular irritation, foreign body sensation, bitter taste
- Infrequent: blepharitis, vision changes, corneal staining, GI disturbance, headache, paraesthesia, dizziness, dermatitis
- Rare: allergic reactions, eg urticaria, angioedema, bronchospasm

**Dosage**
1 drop twice daily.

**Patient counselling**
- Shake bottle before use.
- Your eye may feel uncomfortable for a little while after you have put in the drop. If you have blurred vision, avoid driving or operating machinery until your sight improves.
- After putting in the drop press lightly on the tear duct for 3 minutes; this stops the drop from quickly draining from your eye.
- If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Practice points**
- may be used when beta-blocker is ineffective or not tolerated
- may be used with ophthalmic beta-blockers

**Products**
- BRINZOLAMIDE EYE DROPS 1% (AZOPT®)

DORZOLAMIDE (EYE)

**Mode of action**
Inhibit carbonic anhydrase II (predominant subtype found in the eye) and reduce elevated intraocular pressure.

**Indications**
- Glaucoma
- Ocular hypertension
- Open angle glaucoma

**Contraindications**
- Sulfonamide allergy

**Specific considerations**
- Corneal grafts, endothelial dystrophy: may cause corneal oedema and precipitate corneal decompensation.
- Pregnancy: Avoid use; no human data available; ADEC category B3.
- Lactation: No human data available.

**Adverse effects**
- Common: conjunctivitis and lid reactions
- Infrequent: blurred vision (transient myopia), superficial punctate keratitis
- Rare: inflammation of the iris and ciliary body, neuropsychiatric effects (hallucinations, agitation, depression,
anorexia, dementia)
Common: ocular irritation, foreign body sensation, bitter taste
Infrequent: blepharitis, vision changes, corneal staining, GI disturbance, headache, paraesthesia, dizziness, dermatitis
Rare: allergic reactions, eg urticaria, angioedema, bronchospasm

Dosage
Single agent, 1 drop 3 times daily.
Adjunct to beta-blocker, 1 drop twice daily.

Patient counselling
Your eye may feel uncomfortable for a little while after you have put in the drop. If you have blurred vision, avoid driving or operating machinery until your sight improves.
After putting in the drop press lightly on the tear duct for 3 minutes; this stops the drop from quickly draining from your eye.
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

Practice points
- May be used when beta-blocker is ineffective or not tolerated
- May be used with ophthalmic beta-blockers

Products
DORZOLAMIDE 2 % (AS HCL) + TIMOLOL 0.5 % (AS MALEATE) EYE DROPS (COSOPT®)
DORZOLAMIDE EYE DROPS 2 % (AS HCL) (TRUSOPT®)

11.02.06 OTHER DRUGS FOR GLAUCOMA

ACETAZOLAMIDE (EYE)
Systemic carbonic anhydrase inhibitor

Mode of action
Inhibits carbonic anhydrase and therefore bicarbonate synthesis; in the eye this reduces aqueous humour secretion and intraocular pressure; in the brain this leads to the accumulation of carbon dioxide, reducing the spread of seizure activity.

Indications
Perioperative reduction of intraocular pressure, eg acute closed angle glaucoma
Chronic open angle glaucoma where other treatments have failed

Contraindications
Serious allergy to sulfonamides

Specific considerations
Gout: may exacerbate.

Adverse effects
Up to 50% of patients do not tolerate acetazolamide. Adverse reactions common to sulfonamides may occur.
Common: paraesthesia (of hands, face, feet or mucocutaneous junctions), fatigue, drowsiness, depression, decreased libido, bitter or metallic taste, nausea, vomiting, abdominal cramps, diarrhoea, black faeces, polyuria, renal stones, electrolyte changes (hypokalaemia, hyponatraemia)
Infrequent: transient myopia (ciliary body swelling), bullous skin eruptions (Stevens–Johnson syndrome)
Rare: aplastic anaemia (especially in the first 6 months), thrombocytopenia, agranulocytosis or neutropenia, anaphylaxis

Dosage
Chronic open angle glaucoma
Adult, oral, initially, 125 mg twice daily, increase to a maximum of 250 mg 4 times daily.
Child, oral, 5–10 mg/kg (up to 250 mg) every 6 hours has been used (specialist supervision).

Perioperative reduction of intraocular pressure
Adult, oral/IV, initially, 250–500 mg. Maintenance, 250 mg every 4 hours as required, to a maximum of 1 g daily.
Higher doses are unlikely to result in increased effect.
Renal impairment: Moderate, halve the dose or double the dosing interval.

Administration instructions
Take tablets with meals.
IM injection is painful and not recommended.
Avoid extravasation of IV injection.

Practice points
- Although acetazolamide is still marketed for use as a diuretic in heart failure such use is now obsolete.
11.03 DRUGS FOR ALLERGIC AND INFLAMMATORY EYE CONDITIONS

11.03.01 VASOCONSTRICTORS (EYE)

NAPHAZOLINE (EYE)
NAPHAZOLINE + ANTAZOLINE (EYE)

Mode of action
Alpha-adrenoreceptor agonists constrict conjunctival blood vessels, reducing ocular redness and discomfort.

Indications
- Relief of mild ocular congestion
- Mild ocular congestion

Contraindications
- Narrow anterior chamber angle

Specific considerations
- Pregnancy: Safe to use in short term use (up to 5 days).
- Lactation: Safe to use.

Adverse effects
- Common: rebound hyperemia, stinging on instillation
- Others: mild mydriasis, blurred vision, epithelial erosion, narrowing of the tear duct, acute and chronic conjunctivitis with prolonged use (months), corneal and conjunctival pigment deposition with prolonged use (years)

Dosage
1–2 drops every 6–12 hours as required.

Patient counselling
- Do not use continuously for >5 days.
- Seek medical attention if symptoms do not improve within 48 hours.
- Although advertised as being useful for relieving eye redness due to minor irritations such as dust, smoke and contact lens wear, a cool compress is as beneficial and is safer. Using drops like this for too long can cause symptoms similar to red eyes.
- If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Practice points
- Vasoconstrictor eye drops, used widely in non-prescription products, are not recommended as their benefit is doubtful and rebound hyperaemia leads to overuse

Products
- NAPHAZOLINE 0.05 % + ANTAZOLINE 0.5 % EYE DROPS 10 ML BOTTLE (ANTISTIN PRIVIN®, ALERGOFTALV®)
- NAPHAZOLINE EYE DROPS 0.1 % 10-15 ML BOTTLE (APIZOLIN®, NAPHCON FORTE®)

11.03.02 ANTIHISTAMINES (EYE)

KETOTIFEN (EYE)

Mode of action
- Selective H1 antagonist (antihistamine); ketotifen also stabilises mast cells.

Indications
- Seasonal allergic conjunctivitis
- Allergic conjunctivitis

Contraindications
- Allergy to ketotifen

Specific considerations
- Pregnancy: Avoid use; no human data available; ADEC category B1.
- Lactation: Suitable if needed.

Adverse effects
Infrequent: allergy, blurred vision (on instillation), dry eye, dry mouth, sedation
Common: stinging on instillation, mild eye irritation, headache

**Dosage**
Adult and child >3 years, 1 drop twice daily.

**Patient counselling**
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Products**
**KETOTIFEN EYE DROPS 0.025 MG/ML 5 ML BOTTLE (ZADITEN®)**

**OLOPATADINE (EYE)**

**Mode of action**
Selective H1 antagonist (antihistamine); olopatadine also stabilises mast cells.

**Indications**
Seasonal allergic conjunctivitis
Allergic conjunctivitis

**Specific considerations**
Pregnancy: Avoid use; no human data available; ADEC category B3 (levocabastine); ADEC category B1 (ketotifen, olopatadine).
Lactation: Suitable if needed.

**Adverse effects**
Common: hyperaemia, keratitis, dry eye
Common: stinging on instillation, mild eye irritation, headache

**Dosage**
Adult and child >3 years, 1 drop twice daily.

**Patient counselling**
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Products**
**OLOPATADINE EYE DROPS 0.1 % (PATANOL®)**

**Isospaglumic acid has been used as the sodium salt. It is given as eye drops for allergic eye conditions.**

**Indications**
Allergic conjunctivitis

**Products**
**ISOPAGLUMIC ACID (AS SODIUM SALT) EYE DROPS 38 MG/ML 10 ML BOTTLE (NOT-REGISTERED)**

**11.03.03 MAST CELL STABILIZERS (EYE)**

**CROMOGLYCATE (EYE)**

**Mode of action**
Inhibition of mast cell degranulation by unknown mechanism.

**Indications**
Seasonal allergic conjunctivitis and vernal keratoconjunctivitis
Allergic conjunctivitis or keratoconjunctivitis

**Specific considerations**
Pregnancy: Safe to use; ADEC category A.
Lactation: Safe to use.

**Adverse effects**
Generally well tolerated; stinging on instillation.

**Dosage**
1 drop 4–6 times daily.

**Patient counselling**
These drugs can take 4–6 weeks to reach full effect (except ketotifen and olopatadine).
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Practice points**
• mast cell stabilisers have delayed onset of action (except those with antihistaminic effects); try for at least 2–4 weeks before evaluating effect
• start treatment with cromoglycate 1 month before the onset of the hay fever season, or give with a low potency corticosteroid eye drop, eg hydrocortisone, for the first month for best results

**Products**

**CROMOGLICIC ACID EYE DROPS 4 % (APICROM®, CUSICROM®)**

**LODOXAMIDE (EYE)**

**Mode of action**
Inhibition of mast cell degranulation by unknown mechanism.

**Indications**
Seasonal allergic conjunctivitis and vernal keratoconjunctivitis
Allergic conjunctivitis or keratoconjunctivitis

**Specific considerations**
Pregnancy: Limited data available; ADEC category B1.
Lactation: No data available although short term use should not be of concern.

**Adverse effects**
Common: blurred vision
Generally well tolerated; stinging on instillation.

**Dosage**
Adults and children >4 years, 1 drop 4 times daily.

**Patient counselling**
These drugs can take 4–6 weeks to reach full effect (except ketotifen and olopatadine).
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Practice points**
• mast cell stabilisers have delayed onset of action (except those with antihistaminic effects); try for at least 2–4 weeks before evaluating effect
• start treatment with lodoxamide 1 month before the onset of the hay fever season, or give with a low potency corticosteroid eye drop, eg hydrocortisone, for the first month for best results

**Products**

**LODOXAMIDE EYE DROPS 0.1 % (ALOMIDE®)**

**11.03.04 NSAIDs (EYE)**

**DICLOFENAC (EYE)**

**Mode of action**
NSAIDs inhibit cyclo-oxygenase, decreasing prostaglandin synthesis and prostaglandin-mediated inflammation.

**Indications**
Marketed: Inhibition of miosis during cataract surgery
Prevention of inflammation after cataract surgery
Accepted: Alternative to corticosteroids or as corticosteroid sparing agents (eg episcleritis, inhibition of postoperative inflammation, allergic conjunctivitis); ophthalmologist use only
Analgesia following photorefractive surgery; ophthalmologist use only

**Contraindications**
Aspirin- or NSAID-induced anaphylactoid reactions (eg asthma, urticaria or rhinitis)

**Specific considerations**
Pregnancy: ADEC category C. Short term low dose use should not be a concern.
Lactation: Safe to use.

**Adverse effects**
delayed epithelial growth and wound healing, persistent epithelial defects following keratoplasty
Common: stinging on instillation, ocular irritation
Rare: dyspnoea, exacerbation of asthma

**Dosage**
Anti-inflammatory, analgesic, 1 drop 3–5 times daily.
Perioperative, dose determined by surgeon.

**Patient counselling**
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Practice points**
- these agents have an insignificant effect on intraoperative miosis (marketed indication) and are used more as an alternative or adjuvant to topical corticosteroids
- may mask symptoms of ocular infections

**Products**

**DICLOFENAC EYE DROPS 0.1 % (AS SODIUM) 5 ML BOTTLE (APICLOF®, DICLOPHARM®, DICLOGESIC®, NACLOF®)**

**INDOMETACIN (EYE)**

Indometacin has been used topically as 1% eye drops to prevent miosis during cataract surgery; the usual dose is one drop instilled 4 times daily, beginning on the day before surgery, and one drop 45 minutes before surgery. The eye drops may then be instilled 4 times daily for up to 10 to 12 weeks postoperatively to prevent cystoid macular oedema.

**Adverse effects**
As for NSAIDs in general but more frequent

**Specific consideration**
Breastfeeding: compatible according to American Academy of Pediatrics

**Products**

**INDOMETACIN EYE DROPS 0.1 % 5 ML BOTTLE (INDOCOLLYRE®)**

**KETOROLAC (EYE)**

**Mode of action**
NSAIDs inhibit cyclo-oxygenase, decreasing prostaglandin synthesis and prostaglandin-mediated inflammation.

**Indications**
Short term (2–4 weeks) treatment of seasonal allergic conjunctivitis
Prevention and reduction of inflammation after cataract surgery
Allergic conjunctivitis
Prevention of inflammation after cataract surgery
Accepted: Alternative to corticosteroids or as corticosteroid sparing agents (eg episcleritis, inhibition of postoperative inflammation, allergic conjunctivitis); ophthalmologist use only
Analgesia following photorefractive surgery; ophthalmologist use only

**Contraindications**
Aspirin- or NSAID-induced anaphylactoid reactions (eg asthma, urticaria or rhinitis)

**Specific considerations**
Pregnancy: ADEC category C. Short term low dose use should not be a concern.
Lactation: Safe to use.

**Adverse effects**
Common: local allergic reactions, superficial keratitis
Rare: systemic allergic reactions
Common: stinging on instillation, ocular irritation
Rare: dyspnoea, exacerbation of asthma

**Dosage**
1 drop 4 times daily.

**Patient counselling**
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Practice points**
- start drops 24 hours before cataract surgery, then continue for 2–4 weeks if needed

**Products**

**KETOROLAC EYE DROPS 5 MG/ML 5 ML BOTTLE (ACULAR®)**

**11.03.05 CORTICOSTEROIDS (EYE)**

**DEXAMETHASONE (EYE)**

**Mode of action**
Intracellular receptor-mediated inhibition of inflammatory cascade, fibroblast and keratocyte activity.
Indications
Allergic and selected inflammatory conditions of lids, conjunctiva, cornea, iris and ciliary body, including postoperative inflammation

Contraindications
Ocular infection, especially herpes simplex epithelial keratitis and fungal keratitis

Specific considerations
Contact lens wearers: risk of indiscriminate long term use of corticosteroids to relieve ocular irritation.
Coexisting conditions: Glaucoma—may be aggravated.
Children: Use increases risk of ocular hypertension and cataract.
Pregnancy: Safe to use if indicated.
Lactation: Safe to use.

Adverse effects
Topical ocular corticosteroids (alone or with antibacterials) have major adverse effects which can threaten vision and should not be prescribed without close supervision by, or discussion with, an ophthalmologist.
Common: ocular hypertension (usually reversible) proportional to dose, potency, penetration and duration of treatment; retarded corneal healing, rebound inflammation
Infrequent: opportunistic infection
Rare: refractive changes, ptosis, chemosis, lid swelling, exophthalmos (slowly, incompletely reversible)
Cataracts: Posterior subcapsular cataracts may occur with long term (>1 year) high dose use; mostly asymptomatic and partially reversible.

Dosage
Titrate to disease severity and treatment response.
Usual range, 1 drop 2–4 times daily.
Intensive treatment, 1 drop every hour.

Patient counselling
Shake suspensions before use.
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

Practice points
• do not prescribe ocular corticosteroids for >2 weeks without supervision by an ophthalmologist unless facilities are available to monitor corneal epithelium and intraocular pressure

Products
DEXAMETHASONE EYE DROPS 0.1 %  5 ML BOTTLE (CEBEDEX®, MAXIDEX®, SPERSADEX®)
DEXAMETHASONE EYE OINTMENT 0.5 %  3 GM TUBE (OFTALMOLOLSA DEXAMETHASONE®)

FLUOROMETHOLON (EYE)

Mode of action
Intracellular receptor-mediated inhibition of inflammatory cascade, fibroblast and keratocyte activity.

Indications
Allergic and selected inflammatory conditions of lids, conjunctiva, cornea, iris and ciliary body, including postoperative inflammation

Contraindications
Ocular infection, especially herpes simplex epithelial keratitis and fungal keratitis

Specific considerations
Contact lens wearers: risk of indiscriminate long term use of corticosteroids to relieve ocular irritation.
Coexisting conditions: Glaucoma—may be aggravated.
Children: Use increases risk of ocular hypertension and cataract.
Pregnancy: Safe to use if indicated.
Lactation: Safe to use.

Adverse effects
Topical ocular corticosteroids (alone or with antibacterials) have major adverse effects which can threaten vision and should not be prescribed without close supervision by, or discussion with, an ophthalmologist.
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Rare: refractive changes, ptosis, chemosis, lid swelling, exophthalmos (slowly, incompletely reversible)
Cataracts: Posterior subcapsular cataracts may occur with long term (>1 year) high dose use; mostly asymptomatic
and partially reversible.

**Dosage**
Titrate to disease severity and treatment response.
Usual range, 1 drop 2–4 times daily.
Intensive treatment, 1 drop every hour.

**Patient counselling**
Shake suspensions before use.
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- fluorometholone acetate is more potent than fluorometholone; they are not interchangeable

**Products**
FLUOROMETHOLONE EYE DROPS 0.1% 5 ML BOTTLE (F.M.L®, FLUCON®)

**PREDNISOLONE (EYE)**

**Mode of action**
Intracellular receptor-mediated inhibition of inflammatory cascade, fibroblast and keratocyte activity.

**Indications**
Allergic and selected inflammatory conditions of lids, conjunctiva, cornea, iris and ciliary body, including postoperative inflammation

**Contraindications**
Ocular infection, especially herpes simplex epithelial keratitis and fungal keratitis

**Specific considerations**
Contact lens wearers: risk of indiscriminate long term use of corticosteroids to relieve ocular irritation.
Coexisting conditions: Glaucoma—may be aggravated.
Children: Use increases risk of ocular hypertension and cataract.
Pregnancy: Safe to use if indicated.
Lactation: Safe to use.

**Adverse effects**
Topical ocular corticosteroids (alone or with antibacterials) have major adverse effects which can threaten vision and should not be prescribed without close supervision by, or discussion with, an ophthalmologist.
Common: ocular hypertension (usually reversible) proportional to dose, potency, penetration and duration of treatment; retarded corneal healing, rebound inflammation
Infrequent: opportunistic infection
Rare: refractive changes, ptosis, chemosis, lid swelling, exophthalmos (slowly, incompletely reversible)
Cataracts: Posterior subcapsular cataracts may occur with long term (>1 year) high dose use; mostly asymptomatic and partially reversible.

**Dosage**
Titrate to disease severity and treatment response.
Usual range, 1 drop 2–4 times daily.
Intensive treatment, 1 drop every hour.

**Patient counselling**
Shake suspensions before use.
If you need to use >1 type of eye drop at the same time, wait several minutes between use of each eye drop.

**Practice points**
- do not prescribe ocular corticosteroids for >2 weeks without supervision by an ophthalmologist unless facilities are available to monitor corneal epithelium and intraocular pressure
Products
PREDNISOLONE EYE DROPS 0.12 % (AS ACETATE) 5 ML BOTTLE (APICORT®, PRED MILD®)
PREDNISOLONE EYE DROPS 1 % (AS ACETATE) 5 ML BOTTLE (APICORT FORTE®, ECONOPRED®, PRED FORTE®)
PREDNISOLONE EYE OINTMENT 5 MG/GM (AS PIVALATE) 5 GM TUBE (ULTRACORTINOL®)
PREDNISOLONE+NEOMYCIN SULFATE+POLYMYXIN-B EYE DROPS 10 ML BOTTLE (NEOPRED-P®)

11.04 DRUGS FOR DRY EYE
11.04.01 LUBRICANTS

BALANCED STERIL SALT SOLUTION (EYE)
Usage
Eye irrigation

Products
BALANCED STERIL SALT SOLUTION 250 ML BOTTLE (NOT REGISTERED)
BALANCED STERIL SALT SOLUTION 500 ML BOTTLE (NOT REGISTERED)

OCULAR LUBRICANTS
Lubricant drops may contain carmellose, hypromellose, hydroxyethylcellulose, polyvinyl alcohol, polyethylene glycol or propylene glycol. Polycrylic acid and carbomers are used in gel products; ointments contain liquid paraffin. Hydroxypropylcellulose is used in an ocular drug delivery system.

Mode of action
Artificial tear supplement providing lubrication.

Indications
Dry eye syndrome
Relief of mild ocular irritation (eg viral conjunctivitis, after dust, wind or sun exposure, contact lenses, allergic conjunctivitis)
Exposure keratitis (eg facial nerve palsy)
Neurotrophic keratitis

Specific considerations
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Safe to use.

Adverse effects
Ocular irritation
The frequency of ocular irritation differs slightly with the preservative used. Benzalkonium chloride is an effective preservative but more irritant than cetrimide and polyquaternium preservatives. Chlorbutol is a less effective but less irritating, mildly anaesthetic preservative.

Dosage
Eye drops, 1 drop every 1–12 hours as required.
Eye ointment, at night as required.

Patient counselling
Lubricants can be used safely as often as required.

Practice points
- patients often find a suitable lubricant by trial and error
- encourage regular use of eye drops (eg hourly)
- avoid drops containing preservative if wearing contact lenses
- ocular insert is usually a last resort; it is difficult to insert and often poorly tolerated
CARBOMERS (EYE)
Products
CARBOMERS + VITAMIN A EYE DROPS 0.2 % (NOT REGISTERED)

CARMELLOSE SODIUM (EYE)
Products
CARMELLOSE SODIUM EYE DROPS 0.5-1 % (CELLUVISC®, REFRESH PLUS®)

POLYVINYL ALCOHOL (EYE)
Products
POLYVINYL ALCOHOL EYE DROPS 1.4 % (LIQUIFILM®)

HYPROMELLOSE + DEXTRAN 70 (EYE)
Uses and Administration
Hypromellose has properties similar to those of methylcellulose. Hypromellose is widely used clinically in ophthalmic solutions; it is preferred to methylcellulose since mucilages of hypromellose have greater clarity and usually contain fewer undispersed fibres. Hypromellose is used to prolong the action of medicated eye drops and, either alone or with other viscosity-increasing agents, in artificial tears preparations for the management of dry eye; solutions containing 0.3 to 1% of hypromellose are commonly used. Solutions for contact lens care and for lubricating artificial eyes contain similar concentrations. Hypromellose is also administered intra-ocularly, usually as a 2% solution, as an adjunct in ophthalmic surgery and concentrations of up to 2.5% may be used topically to protect the cornea during gonioscopy procedures.

Ophthalmic surgery.
Intra-ocular hypromellose may be used as a visco-elastic agent to protect the eye during surgery. In cataract extraction it is employed to maintain the anterior chamber and to coat the intra-ocular lens to facilitate its implantation. Although intra-ocular hypromellose is generally considered to be well tolerated, some workers reported an increased incidence of pupil abnormalities (non-reactive semi-dilated pupils) following such use; others did not confirm this. There has also been a report of corneal opacities in a number of patients following the use of intra-ocular hypromellose.

Products
HYPROMELLOSE 3 MG/ML + DEXTRAN 70 1 MG/ML EYE DROPS 10-15 ML BOTTLE (TEARS NATURAL®, DACROLUX®)

SODIUM CHLORIDE SOLUTION (EYE)
Products
SODIUM CHLORIDE SOLUTION 15 ML BOTTLE (SODIUM CHLORIDE® (DIFFERENT COMPANIES))

11.05 DRUGS FOR MYDRIASIS AND CYCLOPLEGIA
11.05.01 ANTICHOLINERGICS

ATROPINE (EYE)
Mode of action
Reversibly block acetylcholine receptors on iris sphincter and ciliary muscle.

Indications
Mydriasis, Cycloplegia
Mydriasis: examination of peripheral lens and retina; prevention or breakdown of posterior synechiae from iritis
Cycloplegia: diagnostic refraction; pain relief in iridocyclitis with aqueous flare; chemical occlusion for treatment of suppression amblyopia; ciliary block glaucoma (rare)

Contraindications
Iris clip intraocular lens implant

Specific considerations
Significant head injury: use only short acting agents with care; consult patient's neurosurgeon or intensive care

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specialist. Always make a note that pupils were dilated intentionally.
Narrow anterior chamber angle: mydriasis may rarely precipitate acute closed angle glaucoma.
Previously treated acute closed angle glaucoma: should be dilated under specialist supervision as not all laser iridotomies remain functional.
Lenticular subluxation: small risk of anterior lens displacement.
Children: Use with extreme caution, if at all, in neonates, preterm infants and children with spastic paralysis or brain damage (increased susceptibility to systemic reactions). One drop of 0.5% atropine can cause systemic effects in infants. In young children, long term cycloplegia may induce amblyopia.
Pregnancy: Safe to use; ADEC category A.
Lactation: Unlikely to cause adverse effects at usual doses.

**Adverse effects**

Common: intolerance to bright light (glare), stinging on instillation (especially 1% cyclopentolate), blurred vision (especially near vision), transient intraocular pressure elevation (especially in pre-existing ocular hypertension)
Infrequent: contact allergic blepharitis (atropine), persistent ocular irritation (mucus discharge, severe watering, superficial punctate keratopathy and characteristically no itch), punctal stenosis with prolonged use (years), insomnia, drowsiness (cyclopentolate)
Rare: systemic toxicity, eg dryness of skin and mouth, fever, facial flushing, tachycardia, irritability, disorientation, ataxia, visual hallucinations, incoherent speech, delirium, psychosis, seizures, hyperactivity (children)

**Dosage**

Diagnostic use: 1 drop repeated after 5 minutes if necessary.
Therapeutic use: See also PHENYLEPHRINE (eye)
Iridocyclitis, 1 drop 3–4 times daily (phenylephrine 10% 3 times daily is occasionally used as an adjuvant).
Postoperative, 1 drop 3–4 times daily.

**Patient counselling**

If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Products**

ATROPINE SULFATE EYE DROPS 0.5 %  10 ML BOTTLE (APITROPIN®, COLICRUSI ATROPINE®)
ATROPINE SULFATE EYE DROPS 1 %  10 BOTTLE (APITROPIN®)
ATROPINE SULFATE EYE OINTMENT 1 %  5 GM TUBE (ATROPIN®)

**CYCLOPENTOLATE (EYE)**

**Mode of action**
Reversibly block acetylcholine receptors on iris sphincter and ciliary muscle.

**Indications**
Mydriasis, Cycloplegia
Mydriasis: examination of peripheral lens and retina; prevention or breakdown of posterior synechiae from iritis
Cycloplegia: diagnostic refraction; pain relief in iridocyclitis with aqueous flare; chemical occlusion for treatment of suppression amblyopia; ciliary block glaucoma (rare)

**Contraindications**
Iris clip intraocular lens implant

**Specific considerations**
Significant head injury: use only short acting agents with care; consult patient's neurosurgeon or intensive care specialist. Always make a note that pupils were dilated intentionally.
Narrow anterior chamber angle: mydriasis may rarely precipitate acute closed angle glaucoma.
Previously treated acute closed angle glaucoma: should be dilated under specialist supervision as not all laser iridotomies remain functional.
Lenticular subluxation: small risk of anterior lens displacement.
Children: Use with extreme caution, if at all, in neonates, preterm infants and children with spastic paralysis or brain damage (increased susceptibility to systemic reactions). One drop of 0.5% atropine can cause systemic effects in infants. In young children, long term cycloplegia may induce amblyopia.
Pregnancy: Safe to use; ADEC category B2.
Lactation: Unlikely to cause adverse effects at usual doses.

**Adverse effects**

Common: intolerance to bright light (glare), stinging on instillation (especially 1% cyclopentolate), blurred vision (especially near vision), transient intraocular pressure elevation (especially in pre-existing ocular hypertension)
Infrequent: contact allergic blepharitis (atropine), persistent ocular irritation (mucus discharge, severe watering,
superficial punctate keratopathy and characteristically no itch), punctal stenosis with prolonged use (years), insomnia, drowsiness (cyclopentolate)

Rare: systemic toxicity, eg dryness of skin and mouth, fever, facial flushing, tachycardia, irritability, disorientation, ataxia, visual hallucinations, incoherent speech, delirium, psychosis, seizures, hyperactivity (children)

**Dosage**

Examine after 20 minutes (30 minutes for darkly pigmented eyes and for cycloplegic refraction).

**Adult:** 1 drop repeated after 5 minutes if necessary.

**Child:** 1–12 years, 1 drop proxymetacaine followed by 1 drop cyclopentolate 1%, repeated in 1 minute.

**Infant <1 year:** 1 drop proxymetacaine followed by 1 drop cyclopentolate 0.5%, repeated in 5 minutes.

**Neonate <1 month:** 1 drop proxymetacaine followed by 1 drop cyclopentolate 0.5%.

**Preterm infant (<32 weeks):** 1 drop proxymetacaine followed by 1 drop cyclopentolate 0.1%.

**Patient counselling**

If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

**Practice points**

- 0.1% cyclopentolate and cyclopentolate-phenylephrine drops are prepared by some hospital pharmacies for use in infants

**Products**

CYCLOPENTOLATE EYE DROPS 0.5 % (AS HCL) 5 ML BOTTLE (NOT REGISTERED)

CYCLOPENTOLATE EYE DROPS 1 % (AS HCL) 10 ML BOTTLE (PENTOLATE®, COLIRCUSI CICLOPLEJICO®)

CYCLOPENTOLATE MINIMS 0.5 % (AS HCL) 0.5 ML MINIMS (NOT REGISTERED)

CYCLOPENTOLATE MINIMS 1 % (AS HCL) 0.5 ML MINIMS (CYCLOPENTOLATE MINIMS®)

**TROPICAMIDE (EYE)**

**Mode of action**

Reversibly block acetylcholine receptors on iris sphincter and ciliary muscle.

**Indications**

- Cycloplegia
- Mydriasis: examination of peripheral lens and retina; prevention or breakdown of posterior synechiae from iritis
- Cycloplegia: diagnostic refraction; pain relief in iridocyclitis with aqueous flare; chemical occlusion for treatment of suppression amblyopia; ciliary block glaucoma (rare)

**Contraindications**

- Iris clip intraocular lens implant
- Specific considerations
- Significant head injury: use only short acting agents with care; consult patient's neurosurgeon or intensive care specialist. Always make a note that pupils were dilated intentionally.
- Narrow anterior chamber angle: mydriasis may rarely precipitate acute closed angle glaucoma.
- Treated acute closed angle glaucoma: should be dilated under specialist supervision as not all laser iridotomies remain functional.
- Lenticular subluxation: small risk of anterior lens displacement.
- Children: Use with extreme caution, if at all, in neonates, preterm infants and children with spastic paralysis or brain damage (increased susceptibility to systemic reactions). One drop of 0.5% atropine can cause systemic effects in infants. In young children, long term cycloplegia may induce mydriasis.
- Pregnancy: Safe to use; atropine ADEC category A; cyclopentolate, homatropine, tropicamide ADEC category B2.
- Breastfeeding: Unlikely to cause adverse effects at usual doses.

**Adverse effects**

- Common: intolerance to bright light (glare), stinging on instillation (especially 1% cyclopentolate), blurred vision (especially near vision), transient intraocular pressure elevation (especially in pre-existing ocular hypertension)
- Infrequent: contact allergic blepharitis (atropine), persistent ocular irritation (mucus discharge, severe watering discharge, superficial punctate keratopathy and characteristically no itch), punctual stenosis with prolonged use (years), insomnia, drowsiness (cyclopentolate)
- Rare: systemic toxicity, eg dryness of skin and mouth, fever, facial flushing, tachycardia, irritability, disorientation, ataxia, visual hallucinations, incoherent speech, delirium, psychosis, seizures, hyperactivity (children)

**Dosage**

Adult, 1 drop repeated after 5 minutes if necessary (add phenylephrine 2.5% if dilation is inadequate).

Examine after 20 minutes (30 minutes for darkly pigmented eyes and for cycloplegic refraction).
11.05.02 OTHER DRUGS FOR MYDIASIS

PHENYLEPHRINE (EYE)

Mode of action
Relatively selective alpha1 agonist; stimulates pupil dilator muscle. Maximal mydriasis occurs after 60–90 minutes; duration of action is 5–7 hours. Does not affect accommodation.

Indications
Marketed: Diagnostic mydriasis
Prevention of posterior adhesions in uveitis
Relief of mild ocular congestion
Accepted: Diagnostic vasoconstriction in episcleritis

Specific considerations
Recent MI, unstable angina: BP elevation with 10% drops may be significant if repeated doses given.
Elderly: Increased risk of systemic adverse effects.
Children: Increased risk of systemic adverse effects, especially hypertension and intraventricular bleeding in the first 2–4 weeks of life in preterm infants. Do not use 10% drops in preterm infants.
Pregnancy: Avoid use; theoretical risk of placental vasoconstriction and fetal hypoxia.
Lactation: Safe to use.

Adverse effects
Common: rebound miosis, hyperaemia, stinging on instillation
Infrequent: liberation of iris pigment (probably has no deleterious effects)
Rare: systemic effects (most frequently with 10% drops), eg hypertension, tachycardia, tremor, anxiety, sweating

Dosage
Generally used as an adjunct.
Mydriasis: 2.5%, 1 drop once only as adjunct if mydriasis difficult, 10%, 1 drop once only as adjunct for rapid maximal mydriasis.
Uveitis: 10%, 1 drop 3 times daily as adjunct to mydriatic.
Episcleritis, diagnosis (vasoconstriction test): 2.5%, 1 drop once only; episcleral vessels should blanch after 5 minutes.

Patient counselling
If you need to use >1 type of eye drop at the same time, wait several minutes between using each eye drop.

Practice points
• reduce systemic absorption by pressing on the tear duct and closing eyes for 3 minutes after instilling drops

Products
PHENYLEPHRINE EYE DROPS 2.5 % (AS HCL) 10 ML BOTTLE (NOT REGISTERED)
PHENYLEPHRINE EYE DROPS 10 % (AS HCL) 10 ML BOTTLE (APIFRIN®)
PHENYLEPHRINE MINIMS 2.5 % (AS HCL) 0.5 ML MINIMS (PHENYLEPHRINE®)

11.06 DRUGS FOR EYE EXAMINATION AND PROCEDURES

11.06.01 LOCAL ANAESTHETICS (EYE)

OXYBUPROCAINE (EYE)

Mode of action
Block nerve conduction reversibly.

Indications
Short term ocular surface anaesthesia

Specific considerations
Prolonged use impairs corneal epithelial healing, prevents reflex ocular protection and masks progression of
keratopathy; use only for short procedures (<20 minutes).
Coexisting conditions: Corneal scrapings: use preservative-free drops (preservative may affect microbiological culture).
Pregnancy: Safe to use (lignocaine ADEC category A, others not categorised).
Lactation: Safe to use.

**Adverse effects**
Common: stinging on instillation, punctate epithelial damage of cornea (do not use long term because of epithelial toxicity, ie acute corneal ulceration)
Rare: allergy

**Dosage**
1 drop, repeated in 5 minutes if necessary.
Maximum 1 drop every 5 minutes for 5 doses.

**Patient counselling**
Warn patients (especially children) about the initial stinging.
Close eyes after instillation and dab away tears without rubbing eyes.

**Practice points**
- never prescribe for home use
- topical anaesthetics increase corneal permeability and intraocular bioavailability of other topical drugs; they also reduce the initial stinging of other topical drugs and should be instilled first
- single use drops are useful if infection is suspected

**Products**
- OXYBUPROCAINE EYE DROPS 0.4 % (NOVESIN®)
- OXYBUPROCAINE MINIMS 0.4 % (AS HCL) 0.5 ML MINIMS (BENOXINATE®)

**TETRACAINE (AMETHOCaine) (Eye)**

**Mode of action**
Block nerve conduction reversibly.

**Indications**
Short term ocular surface anaesthesia

**Specific considerations**
Prolonged use impairs corneal epithelial healing, prevents reflex ocular protection and masks progression of keratopathy; use only for short procedures (<20 minutes).
Coexisting conditions
Corneal scrapings: use preservative-free drops (preservative may affect microbiological culture).
Pregnancy: Safe to use (lignocaine ADEC category A, others not categorised).
Breastfeeding: Safe to use.

**Adverse effects**
Common: stinging on instillation, punctate epithelial damage of cornea (do not use long term because of epithelial toxicity, ie acute corneal ulceration)
Rare: allergy

**Dosage**
1 drop, repeated in 5 minutes if necessary.
Maximum: 1 drop every 5 minutes for 5 doses.

**Counselling**
Close eyes after instillation and dab away tears without rubbing eyes.
These eye drops may sting at first.

**Practice points**
- never prescribe for home use
- topical anaesthetics increase corneal permeability and intraocular bioavailability of other topical drugs; they also reduce the initial stinging of other topical drugs and should be instilled first
- single use drops are useful if infection is suspected

**Products**
- TETRACAINE (AMETHOCaine) MINIMS 1 % (AS HCL) 0.5 ML MINIMS (AMETHOCaine®)

**11.06.02 OCULAR STAINS**
**FLUORESCEIN (EYE)**

**Mode of action**
Fluorescent stain enhances the observation of vascular structure, flow and permeability.

**Indications**
Diagnostic fundus or anterior segment angiography

**Contraindications**
Previous allergic reaction to IV fluorescein

**Specific considerations**
Asthma or history of allergy: may be more likely to experience allergic reaction to IV fluorescein.
Soft contact lenses: may be stained by fluorescein secreted in tears; do not wear lenses for 24 hours after injection.
Pregnancy: Avoid use; limited human data available; known to cross placenta. Contact specialised information service.
Lactation: Known to be excreted in milk; limited experience, contact specialised information service

**Adverse effects**
Common: nausea, headache, vomiting, strong taste (all transient and related to concentration), discolouration of skin (for 12 hours), urine (for 36 hours) and tears
Infrequent: low back pain, moderate allergic reactions, eg urticaria
Rare: severe generalised allergic reaction
Extravasation: Causes severe pain, occasionally superficial phlebitis and subcutaneous granuloma, and rarely sloughing of skin and toxic neuritis.

**Dosage**
Adult: IV 2 mL of 25% (or 5 mL of 10%) solution.
Child: IV 8 mg/kg (ie 0.032 mL/kg of 25% or 0.08 mL/kg of 10% solution).

**Administration instructions**
Use a 21 G cannula and inject as a rapid bolus; avoid extravasation.
Be prepared to manage anaphylaxis.

**Patient counselling**
Fluorescein can cause yellow discolouration of skin, tears and urine and can also stain soft contact lenses. Do not wear lenses for 24 hours after injection.

**Products**
- FLUORESCEIN 0.25 % + LIDOCAINE 4 % MINIMS (M.LIGNOCAINE 4% & FLUORESCEIN 0.25%®)
- FLUORESCEIN SODIUM AMP 10 % (FLUORESCEINE®)
- FLUORESCEIN SODIUM STRIPS (NOT REGISTERED)

**TRYPAN BLUE SOLUTION (EYE)**
Trypan blue solutions are used as stains in microscopy and for visualisation of various tissues as an aid to ophthalmic surgery

**Products**
- TRYPAN BLUE SOLUTION, INTRA OCULAR (NOT REGISTERED)

11.07 DRUGS FOR MACULAR DEGENERATION

**VERTEPORFIN (EYE)**

**Mode of action**
Verteporfin is taken up by the choroidal neovasculature of the eye and generates highly reactive oxygen radicals in the presence of laser light and oxygen. These cause local cytotoxic effects which damage the neovascular epithelium resulting in temporary vessel occlusion.

**Indications**
Treatment of patients with predominantly classic subfoveal choroidal neovascularisation due to age-related macular degeneration or with subfoveal choroidal neovascularisation caused by other macular diseases

**Contraindications**
Porphyria, Allergy to verteporfin, Severe hepatic impairment

**Specific considerations**
Hepatic impairment: Use with caution in moderate hepatic impairment or biliary obstruction.
Elderly: Most people in clinical trials were >60 years; a reduced treatment effect is seen with increasing age.
Adverse effects
Common: abnormal vision, pain, oedema and inflammation at the injection site, back pain, nausea, asthenia, itch, hypercholesterolaemia, photosensitivity evident as sunburn
Infrequent: retinal detachment, subretinal or vitreous haemorrhage, allergy, pain, hypertension, fever, chest pain, vasovagal reactions (procedure related)
Rare: severe allergic reactions
Ocular effects: Abnormal vision including blurring, haziness, decreased vision, black spots, grey or dark haloes.
Severe vision loss occurred in clinical trials (2.1% of the treated group) mainly in those with occult or minimally classic choroidal neovascularisation. Most recovered partly or completely.

Dosage
IV infusion, 6 mg/m2.

Administration instructions
Give over 10 minutes in 30 mL glucose 5% through a free-flowing IV line in the antecubital vein; avoid extravasation (severe pain, inflammation, swelling or discolouration); do not use veins in the back of the hand. 15 minutes after the start of the infusion use a diode laser to deliver non-thermal red light (wavelength 689 nanometres).
If extravasation is suspected stop the infusion immediately; protect the area from bright direct light until swelling and discoulouration have disappeared to prevent burning (which could be severe); put cold compresses on the injection site.
Avoid contact with skin and eyes (risk of photosensitivity); wipe up spills carefully.

Patient counselling
Tell someone immediately if you have any pain, stinging or burning during the injection.
After the treatment you will be very sensitive to sunlight and bright indoor light such as halogen lights and those in dental surgeries or operating theatres. You must avoid exposure of your skin or eyes to such light for 48 hours after the treatment; normal indoor lighting is safe. Don't stay in the dark as indoor light helps get rid of the drug. Wear protective clothing and sunglasses if you have to go outside; sunscreens are not effective. If you need emergency surgery within 48 hours of your treatment, tell your doctor so that your internal tissues can be protected from light as much as possible.
Your vision may get worse for a while after the treatment; do not drive or use machinery if you are affected.

Practice points
• tell the patient to take precautions to avoid photosensitivity
• re-evaluate every 3 months; if fluorescein angiograms show any recurrence or persistence of leakage consider retreatment; up to 9 treatments in 2 years have been used in clinical trials
• it is not known whether retreatment is necessary once vision is stable even if leakage from the neovasculature is still present or if vision deteriorates despite treatment
• it is also unknown how the decrease in rate of loss of vision translates into improvement in daily life
• not recommended for non-neovascular (dry) age-related macular degeneration
• ideally the eye to be treated should have relatively good residual visual acuity (6/36 or better)

Products
VERTEPORFIN VIAL 15 MG (VISUDYNE®)
Table 11–01 Comparison of drug classes for chronic open angle glaucoma

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Effect</th>
<th>Doses per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta-blocker, eg timolol</td>
<td>+++</td>
<td>1–2</td>
</tr>
<tr>
<td>cholinergic, eg pilocarpine</td>
<td>++</td>
<td>4</td>
</tr>
<tr>
<td>topical carbonic anhydrase inhibitor, eg dorzolamide</td>
<td>++</td>
<td>3</td>
</tr>
<tr>
<td>nonselective adrenergic agonist, dipivefrine</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>alpha2 agonist, eg brimonidine</td>
<td>+++</td>
<td>2–3</td>
</tr>
<tr>
<td>systemic carbonic anhydrase inhibitor, acetazolamide</td>
<td>+++</td>
<td>2–4</td>
</tr>
<tr>
<td>prostaglandin analogue, eg latanoprost</td>
<td>+++</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 11–02 Comparison of ocular corticosteroids

<table>
<thead>
<tr>
<th>Drug and form</th>
<th>Potency (1)</th>
<th>Penetration (1)</th>
<th>Intraocular pressure rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrocortisone suspension, 0.5%, 1%</td>
<td>very low</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>hydrocortisone acetate ointment, 0.5%, 1% low</td>
<td>low</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>fluorometholone suspension, 0.1%</td>
<td>mid</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>prednisolone solution, 0.5%</td>
<td>mid</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>prednisolone acetate suspension, 0.5% high</td>
<td>high</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>fluorometholone acetate suspension, 0.1% high</td>
<td>high</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>dexamethasone suspension, 0.1%</td>
<td>high</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

1with intact corneal epithelium

Table 11–03 Comparison of ocular anticholinergics

<table>
<thead>
<tr>
<th>Effect</th>
<th>Peak effect</th>
<th>Duration</th>
<th>Frequency of systemic adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>atropine 1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mydriasis</td>
<td>30–40 minutes</td>
<td>7–10 days</td>
<td>+++</td>
</tr>
<tr>
<td>cycloplegia</td>
<td>3–6 hours</td>
<td>7–14 days</td>
<td></td>
</tr>
<tr>
<td>cyclopentolate 0.5–1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mydriasis</td>
<td>30–60 minutes</td>
<td>1 day</td>
<td>++</td>
</tr>
<tr>
<td>cycloplegia</td>
<td>25–75 minutes</td>
<td>6–24 hours</td>
<td></td>
</tr>
<tr>
<td>homatropine 2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mydriasis</td>
<td>20–30 minutes</td>
<td>6 hours – 4 days</td>
<td>+</td>
</tr>
<tr>
<td>cycloplegia</td>
<td>30–90 minutes</td>
<td>10 hours – 2 days</td>
<td></td>
</tr>
<tr>
<td>tropicamide 0.5–1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mydriasis</td>
<td>20–40 minutes</td>
<td>6 hours</td>
<td>rare</td>
</tr>
<tr>
<td>incomplete cycloplegia</td>
<td>30–40 minutes</td>
<td>2–6 hours</td>
<td></td>
</tr>
</tbody>
</table>
Table 11–04 Comparison of ocular local anaesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Onset of action</th>
<th>Duration (minutes)</th>
<th>Duration of initial sting (seconds)</th>
<th>Punctate epithelial damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>amethocaine ester</td>
<td>20 seconds</td>
<td>20</td>
<td>30</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>oxybuprocaine ester</td>
<td>20 seconds</td>
<td>10–20</td>
<td>10</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>proxymetacaine ester</td>
<td>20 seconds</td>
<td>10–20</td>
<td>10</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>lignocaine amide</td>
<td>2–5 minutes</td>
<td>20–30</td>
<td>30</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
CHAPTER 12 EAR, NOSE AND THROAT (ENT)

12.01 DRUGS FOR EAR INFECTION, OTITIS EXTERNA

CLOTRIMAZOLE (EAR)

Mode of action
Impair biosynthesis of ergosterol for cytoplasmic membrane, inhibiting fungal growth; fungistatic

Indications
Dermatophytoses
Mucocutaneous candidiasis, including paronychia
Pityriasis versicolor
Dermatophytoses
Pityriasis versicolor
Seborrheic dermatitis

Specific considerations
Pregnancy: Safe to use; ADEC category A.
Lactation: Safe to use.

Adverse effects
Topical imidazoles are generally well tolerated.
Infrequent: burning, stinging, itch, erythema
Rare: allergic reactions

Dosage
Apply sparingly twice a day.

Patient counselling
Regular application is essential for successful treatment.
Complete the full treatment course even if signs of infection have disappeared.
Attention to hygiene is important in the management of fungal disease of the feet; after washing, dry feet thoroughly, especially between toes.

Practice points
- continue treatment for 2–4 weeks in dermatophytoses
- use sparingly, especially in intertriginous areas, to avoid maceration
- creams are preferred; powders may be used on feet, moist lesions of the groin and intertriginous areas with creams or to prevent reinfection
- intractable candidiasis may be the presenting symptom of undiagnosed diabetes; appropriate urine and blood tests may be indicated in patients not responding to treatment
- topical imidazoles are not usually successful in treating infections of the nails or hair

Products
CLOTRIMAZOLE EAR DROPS 1 % 10-20 ML BOTTLE (CLOTREX OTIC®, OTOZOL®)

POLYMYXIN B+NEOMYCIN+HYDROCORTISON (EAR)

HYDROCORTISONE ACETATE

NEOMYCIN SULFATE

Neomycin is an aminoglycoside antibiotic used topically in the treatment of infections of the skin, ear, and eye due to susceptible staphylococci and other organisms
Polymyxin B Sulfate
Polymyxin B sulfate is used topically, often with other drugs, in the treatment of skin, ear, and eye infections due to susceptible organisms.
Hydrocortisone possesses anti-inflammatory, anti-allergic and anti-pruritic activity
For topical application polymyxin B is usually available as a 0.1% solution or ointment, in combination with other drugs

Lidocaine Hydrochloride
12.03 DRUGS FOR VESTIBULAR DISORDERS

TINNITUS
Tinnitus may be idiopathic or associated with hearing loss; it can be a prominent feature of Ménière's disease, see Vertigo.

Before starting treatment
It may be associated with common and treatable conditions, eg ear wax or otitis media.
If tinnitus is unilateral refer to an ENT specialist to exclude retrocochlear pathology, eg acoustic neuroma.
Consider drug associations, eg salicylates, NSAIDs, aminoglycosides, loop diuretics, aspartame.

Drug choice
Many different approaches to drug treatment have been tried. There is little evidence of benefit for most interventions.
Tricyclic antidepressants may be of some benefit but their adverse effects may limit use (especially in older patients).

Practice points
- hearing aids may help by increasing awareness of surrounding ambient noise
- there is insufficient evidence to support the use of masking devices (they produce sound to cover tinnitus symptoms)

VERTIGO
It is important to distinguish peripheral pathology (nystagmus and hearing loss usually present) from CNS or inner ear pathology (nystagmus usually absent, hearing loss rare).
In many cases vertigo is mild and self-limiting and a cause will not be found.
There is little evidence of benefit for most drugs used for vertigo.

Special cases
Benign paroxysmal positional vertigo
Severe, short-lasting vertigo induced by certain head positions.
Postural retraining using a sequence of movements called the Epley manoeuvre is useful.
Medication is usually ineffective.
Severe persistent symptoms may require surgery.

Vestibular neuritis (labyrinthitis)
Inflammation of the vestibular nerve, frequently caused by a virus. It is usually self-limiting and may cause severe vertigo associated with nausea, vomiting and nystagmus.
Acute attacks may be treated as for Ménière's disease. Continual vomiting may require IV fluids.

Ménière's disease
Ménière's disease involves recurrent attacks of vertigo, tinnitus and hearing loss. Restrict salt intake and avoid cigarettes, alcohol, caffeine and CNS stimulants.
Prochlorperazine or antihistamines are used for symptomatic relief of acute attacks; avoid long term use. See Antihistamines (antiemetic).
Betahistine, with or without diuretics, may be effective for long term control of vertigo, dizziness or imbalance, but does not improve hearing.
Surgery is an option if medical treatment fails.

BETAHISTINE

Mode of action
Vasodilator, thought to improve blood flow to labyrinth and brain stem.

Indications
Ménière's disease

Contraindications
Phaeochromocytoma
History of peptic ulcer
Asthma (Use with caution)
Porphyria

Specific considerations
Urticaria: may be exacerbated.
Children: Avoid use in children <12 years.
Pregnancy: Limited data; ADEC category B2.
Lactation: Unlikely to be of concern.

Adverse effects
Rare: GI disturbances, headache, fatigue, dizziness, vasodilation, hypotension, bronchospasm, rash, angioedema

Dosage
8–16 mg 3 times a day.

Patient counselling
Response may be rapid or take several weeks.

Products
BETAHISTINE TABS 8 MG (BETASERC®, BETASTIN®)
BETAHISTINE TABS 16 MG (BETASERC®, BETASTIN®)

CINNARIZINE

Adverse Effects and Precautions
As for the sedating antihistamines in general.
There have been rare reports of extrapyramidal symptoms after cinnarizine, sometimes associated with depressive feelings.
High doses of cinnarizine should be used with caution in patients with hypotension because of the possibility of decreasing blood pressure further.

Uses and Administration
Cinnarizine is a piperazine derivative with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders and for the prevention and treatment of motion sickness. It is also used in the management of various peripheral and cerebral vascular disorders.
The usual dose for vertigo and vestibular disorders is 30 mg three times daily by mouth. For motion sickness a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary. Children aged 5 to 12 years are given half the adult dose for both indications. In some countries, a dose of 75 mg once or twice daily has been given for vertigo and vestibular disorders. Doses of 75 mg may also be given 1 to 3 times daily for cerebrovascular disorders and 2 or 3 times daily for peripheral vascular disorders.

Products
CINNARIZINE TABS 25 MG (CINAR®, STUGERON®, VERTIZIN®)
CINNARIZINE TABS/CAPS 75 MG (CEREPAR®, CINAR®, STUGERON FORTE®, VERTIZIN ®)

FLUNARIZINE

Adverse Effects and Precautions
As for the sedating antihistamines in general. Adverse effects also seen with flunarizine include weight gain, extrapyramidal symptoms (sometimes associated with depression), and, rarely, galactorrhoea.
Flunarizine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in in-vitro systems.

Uses and Administration
Flunarizine is the difluorinated derivative of cinnarizine. It has antihistamine, sedative, and calcium-channel blocking activity. Flunarizine hydrochloride is used for migraine prophylaxis, for vertigo and vestibular disorders, and for peripheral and cerebral vascular disorders. It has also been used as adjunctive antiepileptic therapy in patients refractory to standard regimens.
Flunarizine is given by mouth as the hydrochloride although doses are expressed in terms of the equivalent amount of flunarizine. Flunarizine hydrochloride 11.8 mg is approximately equivalent to 10 mg of flunarizine. The usual dose is 5 to 10 mg daily, usually given at night to minimize the effects of drowsiness.
Epilepsy: Flunarizine has demonstrated antiepileptic activity in animal models, but the mechanism of action is unclear; calcium entry blockade or an effect on sodium channels has been postulated.
Migraine: Flunarizine reduces the frequency of migraine attacks in both adult and paediatric patients and is used for the prophylaxis of migraine in some countries. Its effects are comparable with several other prophylactic antimigraine drugs, including those generally preferred, pizotifen and propranolol

570
Vertigo: Antihistamines are the mainstay of the treatment of vertigo. However, their antimuscarinic side-effects may prove troublesome, particularly in the elderly, and they produce central sedation. Flunarizine is devoid of antimuscarinic properties, although it may produce central sedation.

**Products**

**FLUNARIZINE CAPS 5 MG (SIBELIUM®)**

### 12.04 DRUGS FOR RHINITIS AND SINUSITIS

**RHINITIS**

Rhinitis is an inflammation of the lining of the nose causing congestion, rhinorrhoea, sneezing and itching; classified as acute (infectious), allergic (hay fever) or other (including drug-induced, irritant, occupational).

#### Acute rhinitis

Usually viral (common cold); no specific treatment has been found to be effective.

Steam inhalations and sodium chloride 0.9% nose drops or spray may help to thin nasal secretions and decrease nasal congestion and irritation.

Oral decongestants may help; intranasal decongestants should be used only for a limited time (eg 4–5 days) due to risk of rebound mucosal congestion, which may take several weeks to resolve.

Use of antihistamines or corticosteroids is not indicated.

#### Allergic rhinitis

Seasonal or perennial symptoms, eg sneezing and rhinorrhoea, are due to a type 1 hypersensitivity reaction.

Where possible, identify and avoid allergen.

Usually a combination of drugs is required to relieve symptoms.

**Drug choice**

See Table 12-03 Symptomatic treatment of allergic rhinitis in adults (If this table is to be added, then it should be renamed eg 12.1)

Intranasal corticosteroids are first line treatment in moderate to severe cases; a combination of an intranasal antihistamine with an intranasal decongestant (if needed) is an effective alternative.

Intranasal corticosteroids reduce inflammation and decrease mucus production. Although maximum effect is achieved after several days of regular use, they have an effect on symptoms such as blocked nose and rhinorrhoea within 3–7 hours of starting treatment. They are still effective if used on an as-needed basis.

Intranasal antihistamines are less effective than intranasal corticosteroids; treatment with an intranasal decongestant (4–5 days) may also be needed to control symptoms.

Oral antihistamines, sedating antihistamines and less sedating antihistamines appear to be equally effective, but are less effective than other treatments.

Intranasal mast cell stabilisers, eg cromoglycate, may be preferred to corticosteroids in children.

Intranasal anticholinergics, eg ipratropium, may be useful when rhinorrhoea is the dominant problem.

Oral corticosteroids (short course) are used rarely for disabling symptoms or if polyps are present (see Prednisone/prednisolone).

Decongestants reduce nasal congestion but have no effect on other symptoms. Oral decongestants commonly cause symptoms of CNS stimulation, eg insomnia, irritability. Prolonged use of intranasal agents causes rebound congestion. However, short term treatment (4–5 days) may be useful (with other treatments) if congestion is a problem.

Desensitization may be tried if an allergen is identified and other treatments have failed.

**Other causes of rhinitis**

Include environmental irritants (eg heat, cold, smoke, dust); hormonal causes (no treatment advised during pregnancy); drug-induced rhinitis (eg beta-blockers, oral contraceptives, aspirin, NSAIDs, ACE inhibitors); diet (eg alcohol, spicy foods); and emotional factors.

Response to drug treatment is variable. Management involves identifying and avoiding precipitating factors.

Ensure symptoms are not due to excessive use of intranasal decongestants, causing rebound congestion.

Oral decongestants, intranasal corticosteroids and, in some cases, ipratropium nasal spray, may be useful if non-drug measures fail.

**SINUSITIS**

**Acute sinusitis**

Acute sinusitis is often viral or allergic and may be managed symptomatically.

Analgesics, eg paracetamol or NSAIDs, relieve pain and fever. Steam inhalations, intranasal or oral decongestants, or sodium chloride 0.9% nasal drops and sprays may increase drainage of exudate and improve symptoms.

Consider antibacterials if there is: poor response to decongestants, maxillary toothache, tenderness over the sinuses,
headache, mucopurulent discharge for >1 week or prolonged fever. Amoxicillin is preferred in uncomplicated cases. Seek ENT specialist advice if:

- there is poor response after 5–7 days of antibacterial treatment
- signs of abscess formation or infection spread beyond sinuses
- frequent acute attacks, eg 3–6 per year (depending on severity), or persistent (chronic) symptoms.

**Chronic sinusitis**
Continued symptoms require further investigation. Anaerobic bacteria and/or chronic allergic rhinitis may be involved. Management may include local or systemic corticosteroids, decongestants, antihistamines, nasal lavage, antibacterials, and/or surgery.

### 12.04.01 NASAL SYMPATHOMIMETIC DECOSGESTANTS

**XYLOMETAZOLINE**

**Mode of action**
Produce vasoconstriction in nasal mucosa; decrease nasal blood flow and congestion.

**Indications**
Relief of nasal congestion associated with acute and chronic rhinitis, common cold, sinusitis
Facilitate intranasal examination

**Contraindications**
MAOI treatment

**Specific considerations**
Children: Avoid use in infants <6 months as rebound congestion may cause breathing difficulty. CNS effects are more common in children.

**Adverse effects**
Rarely associated with systemic effects.
Common: transient burning, stinging, increased nasal discharge, rebound congestion with prolonged use (4–5 days)
Rare: hypertension, nausea, nervousness, dizziness, drowsiness, insomnia, headache

**Dosage**
Adult, child >12 years: Nasal drop 0.1%, 2–3 drops into each nostril up to 3 times daily.
Child >6 years: Nasal drop 0.05%, 2–3 drops into each nostril up to 3 times daily.
Child 6 months – 6 years: Nasal drop 0.05%, 1 drop into each nostril up to 3 times daily.

**Practice points**
- encourage use of sodium chloride 0.9% solution (nasal drops, irrigation or spray) in preference to a topical sympathomimetic, especially for children
- do not use in infants <6 months of age; if nasal congestion impairs feeding, use sodium chloride 0.9% nose drops (a few drops in each nostril just before feed) to loosen and liquefy mucus secretions
- keep dose and length of treatment to a minimum (maximum duration of treatment 5 days) to reduce risk of rebound congestion (may take several weeks to reverse)
- oral products, eg pseudoephedrine, are preferred for prolonged use

**Products**
XYLOMETAZOLINE NASAL DROPS 0.05% (AS HCL) 10 ML BOTTLE (DECOZAL®, DECOZOLINE®, OTRIVIN®)
XYLOMETAZOLINE NASAL DROPS 0.1% (AS HCL) 10 ML BOTTLE (DECOZAL®, DECOZOLINE®)

### 12.04.02 CORTICOSTEROIDS (NASAL)

**BUDESONIDE (NASAL)**

**Mode of action**
Produce local anti-inflammatory effects, decrease capillary permeability and mucus production, and produce vasoconstriction in the nasal mucosa.

**Indications**
Rhinitis (allergic and non-allergic)
Nasal polyposis
Nasal polyposis (beclomethasone, budesonide, fluticasone)
Contraindications
Severe nasal infection
Allergy to particular corticosteroid

Specific considerations
Bleeding disorders: may cause nose bleeding.
Recent nasal surgery or trauma: may delay healing.
Pregnancy: Safe to use.
Lactation: Safe to use.

Adverse effects
Systemic adverse effects are rare with nasal preparations used at recommended doses.
Common: nasal stinging, itching, sneezing, sore throat, dry mouth, cough
Infrequent: nose bleed
Rare: nasal septal perforation, glaucoma, cataract, allergic reactions (urticaria, angioedema, bronchospasm, rash)

Dosage
Allergic rhinitis: Adult, child >6 years, initially 128 micrograms into each nostril once daily or 64 micrograms into each nostril twice daily; maintenance 32–64 micrograms into each nostril once daily.
Nasal polyps: Adult, 64 micrograms into each nostril twice daily.

Practice points
• nasal corticosteroids are similarly effective
• onset of action within 3–7 hours; effective on an as-needed basis; optimum effect after several days of regular use
• patients transferred from oral to nasal corticosteroids may have impaired adrenal function; nasal corticosteroids have little systemic effect

Products
BUDESONIDE NASAL SPRAY 100 MCG/DOSE (AQUA) 200 DOSE (ESONIDE®)

FLUTICASONE (NASAL)

Mode of action
Produce local anti-inflammatory effects, decrease capillary permeability and mucus production, and produce vasoconstriction in the nasal mucosa.

Indications
Allergic rhinitis (spray)
Nasal polyps (drops)
Rhinitis (allergic and non-allergic)
Nasal polyps (beclomethasone, budesonide, fluticasone)

Contraindications
Severe nasal infection
Allergy to particular corticosteroid

Specific considerations
Bleeding disorders: may cause nose bleeding.
Recent nasal surgery or trauma: may delay healing.
Pregnancy: Safe to use.
Lactation: Safe to use.

Adverse effects
Systemic adverse effects are rare with nasal preparations used at recommended doses.
Common: nasal stinging, itching, sneezing, sore throat, dry mouth, cough
Infrequent: nose bleed
Rare: nasal septal perforation, glaucoma, cataract, allergic reactions (urticaria, angioedema, bronchospasm, rash)

Dosage
Allergic rhinitis: Adult, child >12 years, initially 2 sprays into each nostril once daily, then 1 spray into each nostril once daily.
Nasal polyps: >16 years, instil drops from 1 container into both nostrils, once or twice daily.

Practice points
• nasal corticosteroids are similarly effective
• onset of action within 3–7 hours; effective on an as-needed basis; optimum effect after several days of regular use
patients transferred from oral to nasal corticosteroids may have impaired adrenal function; nasal corticosteroids have little systemic effect.

**Products**

**FLUTICASONE NASAL SPRAY 50 MCG/DOSE (AS PROPIONATE) 120 DOSE BOTTLE (FLIXONASE®)**

12.04.03 OTHER DRUGS (Nasal)

**DIMETINDENE + PHENYLEPHRINE**

Dimetindene maleate, an alkylamine derivative, is a sedating antihistamine; it is mildly sedative and is reported to have mast-cell stabilising properties. It is used for the symptomatic relief of allergic conditions including urticaria and angioedema and rhinitis, and in pruritic skin disorders. It is also used in compound preparations for the symptomatic treatment of coughs and the common cold.

Dimetindene maleate is applied topically as a 0.1% gel or lotion although, as with other antihistamines, there is a risk of sensitisation. It is used in a strength of 0.025% in compound nasal preparations.

**Products**

**DIMETINDENE 0.025 GM+PHENYLEPHRINE 0.25 GM NASAL GEL (VIBROCIL®)**

**DIMETINDENE 0.025 GM+PHENYLEPHRINE 0.25 GM NASAL SPRAY (VIBROCIL®)**

**IPRATROPIUM (NASAL)**

**Mode of action**

Dries nasal secretions and may reduce rhinorrhea associated with non-allergic rhinitis.

**Indications**

Rhinorrhea associated with allergic and non-allergic rhinitis, and common cold

**Contraindications**

Allergy to ipratropium

**Specific considerations**

Narrow angle glaucoma: may exacerbate.

Pregnancy: Safe to use; ADEC category B1.

Lactation: Safe to use.

**Adverse effects**

Common: nasal dryness, nosebleed, dry mouth, altered taste

Rare: visual accommodation disturbance, urinary retention, allergic reactions (urticaria, angioedema, rash, bronchospasm)

**Dosage**

Rhinorrhea (allergic or non-allergic rhinitis)

For adults and children >12 years.

Initially 42–84 micrograms into each nostril 2–3 times daily, then reduce dose as rhinorrhea improves.

Rhinorrhea (common cold)

Initially 84 micrograms into each nostril 3–4 times daily, then reduce dose as rhinorrhea improves; use for up to 4 days.

**Products**

**IPRATROPIUM NASAL SPRAY 0.03 % (21 MCG/DOSE) 180 DOSE BOTTLE (ATROVENT®)**

12.05 DRUGS ACTING ON THE OROPHARYNX

**CHLORHEXIDINE MOUTH WASH**

**Adverse Effects and Treatment**

Skin sensitivity to chlorhexidine has occasionally been reported. Strong solutions may cause irritation of the conjunctiva and other sensitive tissues. The use of chlorhexidine dental gel and mouthwash has been associated with reversible discoloration of the tongue, teeth, and silicate or composite dental restorations. Transient taste disturbances and a burning sensation of the tongue may occur on initial use.

The main consequence of ingestion is mucosal irritation and systemic toxicity is rare.
**Precautions**

Oral hygiene.

As toothpastes may contain anionic surfactants such as sodium laurilsulfate, which are incompatible with chlorhexidine, it has been recommended that at least 30 minutes should be allowed to elapse between the use of toothpaste and oral chlorhexidine preparations.

**Uses and Administration**

Chlorhexidine is a bisbiguanide antiseptic and disinfectant that is bactericidal or bacteriostatic against a wide range of Gram-positive and Gram-negative bacteria. It is more effective against Gram-positive than Gram-negative bacteria, and some species of Pseudomonas and Proteus have low susceptibility. It is relatively ineffective against mycobacteria. Chlorhexidine inhibits some viruses and is active against some fungi. It is inactive against bacterial spores at room temperature. Chlorhexidine is most active at a neutral or slightly acid pH.

Chlorhexidine is formulated as lotions, washes, and creams for disinfection and cleansing of skin and wounds, and as oral gels, sprays, and mouthwashes for mouth infections including candidiasis and to reduce dental plaque accumulation.

**Mouth disorders.**

Chlorhexidine mouthwashes, sprays, and gels are used to prevent accumulation of dental plaque (see Mouth Infections). Studies have generally shown chlorhexidine mouthwash 0.1 to 0.2% used 2 or 3 times daily to be effective in reducing plaque accumulation and gingivitis,1-4 and to be superior to other disinfectant mouthwashes.5 Its effect against subgingival plaque bacteria is enhanced by phenoxyethanol.6 However, a 1% gel used nightly as a toothpaste was not more effective than placebo in reducing gingivitis in children.7 Other studies have shown that chlorhexidine reduces gingivitis by 60 to 90% but its use is limited by its unpleasant taste and staining properties; special circumstances in which chlorhexidine is helpful include management of acute gingivitis, control of periodontal involvement in immunocompromised patients, and promotion of healing after periodontal treatment. Chlorhexidine gluconate may be useful in controlling secondary bacterial infections of aphthous ulcers (see Mouth Infections). Chlorhexidine may be a useful adjunct to antifungal treatment of oral candidiasis.

**Oral ulceration**

Identify cause (trauma, nutritional deficiency, immunosuppression, dermatological disease, drugs, infection, eg herpes simplex, coxsackie viruses, Candida, syphilis) and treat cause when possible; however, cause is often unknown and in many cases healing occurs spontaneously (usually within 10–14 days). Therapeutic agents may reduce inflammation (local corticosteroids, eg triamcinolone paste); reduce pain at the site (local anaesthetics, eg lignocaine, benzocaine; anti-inflammatory, eg benzydamine), or protect the ulcerated area. There are a number of OTC combination products available. Consider neoplasia in non-healing ulcers (present for >3 weeks).

**Sore throat**

Commonly caused by a virus; occasionally the cause is bacterial (typically streptococcal). Preparations for symptomatic relief often combine anaesthetic and antiseptic agents in a lozenge, gargle or spray. There is little evidence of benefit. Group A beta-haemolytic streptococci are a more common cause of sore throat in children than in adults. If group A streptococcal pharyngitis (fever, tonsillar exudate, cervical lymphadenopathy, absence of cough) is considered likely, then it is reasonable to start antibiotics (phenoxymethylpenicillin is first choice) as symptom duration and complications may be reduced. (If this table is to be added, then it should be renamed eg 12.2). I prefer not to have it.

**Recurrent tonsillitis in children**

Recurrent sore throat is common in childhood and usually has a viral cause. Recurrent tonsillitis is often over-diagnosed. Throat swab during an acute episode can help to guide diagnosis and management. Although a number of approaches have been used to treat true recurrent tonsillitis, including long term low dose penicillin or other antibiotic (eg a cephalosporin or macrolide), there is no good evidence of benefit for these.

**Tooth decay (caries)**

Regular brushing and flossing and avoiding sugary foods and smoking (reduces saliva) are important in preventing tooth decay. Fluoride encourages tooth enamel to repair itself. Fluoride mouth rinses may reduce tooth decay in children even when fluoridated water and toothpaste are used.

**Products**

CHLOROHEXIDINE MOUTH WASH SOLUTION 0.2 (AS GLUCONATE) (NOT REGISTERED)
**MICONAZOL (ORAL GEL)**
See also Miconazole Skin preparations

**Products**
**MICONAZOLE ORAL GEL 2 % (AS NITRATE) 40 GM TUBE (CANDIZOL®, DAKTARIN®, MECONAZOL®, MICOVER®, MYCOHEAL®)**

**NYSTATIN (ORAL)**

**Mode of action**
Polyene antifungals bind to ergosterol in fungal cell membranes altering their permeability and allowing leakage of intracellular components.

**Indications**
Marketed: Treatment of mucocutaneous candidiasis, Treatment and suppression of intestinal candidiasis
Accepted: Prophylaxis against candidiasis in immunocompromised people

**Specific considerations**
Pregnancy: Safe to use; GI absorption negligible; ADEC category A.
Breastfeeding: Safe to use.

**Adverse effects**
Common: nausea, vomiting, diarrhoea (mild with usual doses but more severe with high doses, eg 5 million units daily)

**Dosage**
Intestinal candidiasis: Adult, child, oral, 500 000–1 000 000 units 3 times daily (tablet/capsule).  
Treatment and prophylaxis of oral candidiasis: Adult, child, oral, 100 000 units 4 times daily (oral liquid/lozenge).

**Patient Counselling**
It is best to use the oral liquid or lozenge after (rather than before) a meal or drink. Swish the liquid around the mouth for as long as comfortable before swallowing. Continue to use for about 2 days after your symptoms disappear.

**Practice points**
- nystatin suspension is effective treatment for minor oral fungal infections
- treatment with oral itraconazole or fluconazole is often required in immunocompromised people (especially with HIV)

**Products**
**NYSTATIN SUSP. 100,000 IU/ML  60 ML BOTTLE (MYCOSTAT®, MYCOSTATIN®, MYCOPHIL®)**

**TRIMCINOLONE (ORAL)**

**Adverse Effects, Treatment, and Precautions**
When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

**Hypersensitivity.**
Local reactions to topical triamcinolone preparations have been attributed to the content of ethylenediamine.

**Uses and Administration**
Triamcinolone is a corticosteroid with mainly glucocorticoid activity.
For administration by mouth triamcinolone is used in doses of 4 to 48 mg daily although daily doses over 32 mg are seldom indicated.

**Rhinitis.**
Triamcinolone is used in the management of allergic rhinitis. However, the use of depot injections of triamcinolone to manage seasonal allergic rhinitis has been deemed unacceptable by some

**Products**
**TRIAMCINOLONE ACETONIDE ORAL PASTE 0.1 % (TRIAMCINOLONE ACETONIDE ORAL PASTE 0.1 %)**
CHAPTER 13 DERMATOLOGICAL DRUGS

13.01 DRUGS FOR ECZEMA

ECZEMA

Eczema (dermatitis) includes a wide range of conditions characterised by skin inflammation.
Principal features include itch, redness, scaling and excoriations.
Eczema may be classified as endogenous or exogenous (which requires removal of precipitating factors).
The principles of management are generally the same irrespective of cause.

Rationale for drug use

Relieve symptoms.
Optimise skin hydration.
Suppress inflammation.
Prevent or eliminate infection.

Before starting treatment

Identify and eliminate potential trigger factors including:

- environmental irritants, eg wool, synthetic clothing, soaps, detergents (including bubble bath), carpets, sand, grass, raised temperatures, sweating
- environmental allergens, eg preservatives, fragrances, deodorants, lanolin, nickel, photosensitising drugs, animal hair, inhaled allergens.

A link between food allergens and eczema has not been confirmed. Exclusion diets are controversial and should only be considered after immunological assessment and advice from a dietitian.
The role of house dust mites in eczema and other non-pulmonary conditions is unclear. There is evidence that control of house dust mite reduces severity of symptoms, especially in patients with positive mite RAST scores or skin prick testing, but only if very low levels of mite are achieved. Covering bedding is the most effective control method.
Time to resolution following removal of trigger depends on numerous factors and, while usually rapid, may take up to 3 weeks or more.

Treatment

Hydration: Use tepid rather than hot water, bath oil or colloidal oatmeal (eg DermaVeen®), and soap substitutes; if soaps are used they should have a neutral pH (mild soaps) and time spent bathing should be minimised to reduce resultant dehydration.
Soaking baths (containing bath oil or colloidal oatmeal) of 10–15 minutes duration may be taken once a day in the maintenance treatment of moderate-to-severe eczema and up to 4 times a day during disease flares to remove crusts and dry blisters.
Wet compresses: Wet compresses are usually soaked in tap water. Solutions of aluminium acetate (Burow's solution) or potassium permanganate (Condy's crystals) may be used, but are usually reserved for acute infected eczema. Immediately after hydration and applying emollient and/or topical corticosteroids, apply wet compresses for 15–60 minutes to increase the benefits of topical treatment. Reserve wet compresses for severely affected or persistent areas of eczema (exudative or crusting lesions); inappropriate use may lead to secondary infection (folliculitis), maceration or excessive dryness.

Moisturisers

Moisturisers may prevent exacerbation of eczema already under optimal control; apply liberally at least twice a day; most effective when applied after bathing (water content of skin is at its greatest).
Apply moisturisers 10–15 minutes before topical corticosteroids.
Creams and ointments are more effective than lotions; lotions may be substituted as condition improves. Lotions can be applied without friction and are more cosmetically acceptable.

Topical corticosteroids

Use corticosteroids where moisturisers do not provide adequate relief. The patient's age, site of involvement and disease extent determine the type and strength of preparation and method of application; use the least potent preparation required to bring disease under control.

Topical immunomodulators

Pimecrolimus is marketed as an alternative to corticosteroids for short term or intermittent treatment of mild-to-moderate eczema. Data comparing pimecrolimus with mild or moderate potency corticosteroids in either children or adults are limited. Its place in therapy is presently unclear. It is best reserved for patients >2 years of age as there are
some concerns about toxicity in infants.
Tacrolimus ointment is marketed overseas (as 0.03% and 0.1% ointment). Trial data indicate that it may be as effective as potent corticosteroids but it is expensive.

**Tar and ichthammol**
Have longer lasting anti-inflammatory properties and fewer adverse effects than topical corticosteroids, but are less potent and messier to use, leading to reduced compliance; should not be applied to acutely inflamed skin, face, flexures or genitals because of the potential for irritation; useful for chronic or lichenified lesions.

**Antihistamines**
Although commonly believed to have antipruritic effects, their therapeutic value is primarily due to their sedative properties; newer, less sedating antihistamines are of little value, unless allergic triggers are involved, eg house dust mite.
Sedating antihistamines are useful at night in patients having trouble getting to sleep or waking regularly because of excessive itching.
May be used as short term adjuvants to topical corticosteroid treatment.

**Systemic immunomodulators**
May be used for patients with severe, disabling disease unresponsive to other treatment; their use should be initiated and monitored by a dermatologist.
Systemic corticosteroids are useful in controlling widespread disease and severe generalised disease flares; they produce dramatic clinical improvement but may be associated with rebound flaring after stopping; they should be avoided in children, to reduce the risk of permanent growth retardation.
Cyclosporin may be used; azathioprine and other immunomodulating drugs have also been used.

**Phototherapy**
UVB phototherapy and photochemotherapy (methoxsalen and ultraviolet A irradiation, PUVA) are effective in unresponsive eczema, but there are concerns about long term safety.

**Other treatment**
Oral evening primrose oil has been claimed to be effective in atopic disease, but studies have shown no therapeutic benefit.
Herbal and complementary medicines have been used, but product quality may be variable; there are reports of hepatotoxicity and of potent corticosteroid contaminants.
Dietary manipulation, prolonged breastfeeding of predisposed infants and dietary restriction of breastfeeding mothers have unknown efficacy. Dietary restriction may lead to vitamin deficiency, particularly in children.

**Special cases**
Atopic dermatitis: Occurs in genetically predisposed individuals; diagnosed by the presence of atopy and the pattern and distribution of eczema. Generally managed by keeping skin hydrated and using topical therapy (especially moisturisers) for symptomatic relief.
Limit topical corticosteroid to sites of inflammation.
Nappy dermatitis: Advise parents to use highly absorbent disposable nappies, change nappies frequently, avoid use of plastic pants (because of occlusive effect) and maximise nappy free periods. Applying a protective agent (eg zinc or dimethicone cream) after each nappy change is also useful. Topical hydrocortisone can be used in more severe cases or when the above measures are inadequate.
Nappy dermatitis may be complicated by candidal infection. Treat such infections with a topical azole or nystatin and topical hydrocortisone.
Secondary infection: Treat according to the cause, whether bacterial (usually S. aureus), viral or fungal.
Seborrhoeic dermatitis in adults: Regular use of shampoo containing ketoconazole, miconazole, selenium sulfide, pyrithione zinc, ciclopirox or coal tar is the mainstay of treatment; can also be applied to eyebrows, ears, central face and trunk.
Coal tar preparations containing salicylic acid and/or sulfur may be used to reduce scale.
Topical corticosteroids may be used to reduce inflammation and itch, but should not be used long term. They may also be used intermittently in combination with a topical antifungal agent.

**13.01.01 Corticosteroids (Skin)**

**BETAMETHASONE (SKIN)**

**Mode of action**
Anti-inflammatory, immunosuppressive and antimitotic activity against cutaneous fibroblasts and epidermal cells. They also cause vasoconstriction which has been used to measure their potency.
Useful in a range of skin conditions including insect bite reactions, sunburn and as adjuncts to other treatments.
Indications
Inflammatory skin conditions, eg eczema, and psoriasis

Contraindications
Rosacea
Acne vulgaris
Allergy to corticosteroids or preservatives in vehicle
Ulcerative conditions and/or impaired circulation
Uncontrolled infection in area to be treated

Specific considerations
Pregnancy: Use the lowest potency for the shortest time necessary where emollients and other simple measures are inadequate; ADEC category A.
Skin atrophy: increases systemic absorption and skin atrophy; avoid use.
Diabetes: systemic absorption increases blood glucose; avoid extensive use.
Impaired T cell function: systemic absorption results in immunosuppression; avoid extensive use.
Elderly: Skin atrophy makes cutaneous adverse effects more likely.
Children: More susceptible to systemic absorption due to higher surface area/bodyweight ratio.

Hydrocortisone is adequate initial treatment for most children with mild-to-moderate disease. Use stronger preparations for short periods under close supervision.
Consider a corticosteroid-free period of at least 2 weeks after each 2–3 week period of daily use.
Lactation: Safe to use; ensure breast area is free of corticosteroid before nursing.

Adverse effects
Relative potency, patient age, site and extent of disease, preparation type, method of application and length of treatment determine the incidence and severity of adverse effects.
Common: folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, striae, purpura, depigmentation, telangiectasia
Infrequent: allergic contact dermatitis
Rare: hyperaesthesia, subcutaneous tissue atrophy, systemic effects (hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, growth retardation, Cushing’s syndrome, cataract)

Dosage
Apply sparingly 1–2 times a day.

Practice points
- use an appropriately potent preparation for the shortest time required to control skin disorder then stop corticosteroid
- therapy can be staged (eg remove precipitating factors and use a moisture care plan, then add topical corticosteroids, sedating antihistamines and tar, in order) with the aim of using the fewest number of treatments to control the disease
- apply sparingly in thin layers by smoothing gently into skin, preferably after bathing
- avoid tolerance by applying corticosteroid on alternate days or instituting medication-free periods (eg 5 days on then 2 days off) during treatment of chronic dermatoses

Nappy dermatitis
- treat with a mild topical corticosteroid initially
- advise parents to use highly absorbent disposable nappies and change nappy frequently; avoid plastic pants because of occlusive effect; nappy free periods should be maximised
- use a protective agent (eg zinc cream)
- often complicated by candidal infection (treat with a topical antifungal).

Products
BETAMETHASONE CREAM 0.1 % (AS VALERATE)  30 GM TUBE (BETAVAL®, BETNOVATE®, VALEDERM®)
BETAMETHASONE LOTION 0.1 % (AS VALERATE)  20 ML BOTTLE (BETNOVATE®)
BETAMETHASONE OINTMENT 0.1 % (AS VALERATE)  30 GM TUBE (BETAVAL®, BETNOVATE®)
BETAMETHASONE SCALP LOTION 0.1 % (AS VALERATE)  30 ML BOTTLE (BEMETSON®, BETNOVATE SCALP APPLICATION®)
**CLOBETASOL (SKIN)**

**Mode of action**
The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin, while inflammation and/or other disease processes in the skin may increase percutaneous absorption. Greater absorption was observed for the clobetasol propionate gel formulation as compared to the cream formulation in in vitro human skin penetration studies.

**Usage**
Clobetasol is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

**Contraindications**
Clobetasol is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

**Precautions**
General: Clobetasol propionate is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 g per day.

Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on therapy.

Patients receiving a large dose applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, a.m. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA suppression.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur that require supplemental systemic corticosteroids.

Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios.

If irritation develops, Clobetasol should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used.

If a favorable response does not occur promptly, use of Clobetasol should be discontinued until the infection has been adequately controlled.

Clobetasol should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

Lactation: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Clobetasol is administered to a nursing woman.

Children: Safety and effectiveness of Clobetasol in children and infants have not been established; therefore, use in children under 12 years of age is not recommended. Because of a higher ratio of skin surface area to body mass, children are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.
HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

**Adverse effects**
In a controlled trial with Clobetasol, the only reported adverse reaction that was considered to be drug related was a report of burning sensation (1.8% of treated patients).

In larger controlled clinical trials with other clobetasol propionate formulations, the most frequently reported adverse reactions have included burning, stinging, irritation, pruritus, erythema, folliculitis, cracking and fissuring of the skin, numbness of the fingers, skin atrophy, and telangiectasia (all less than 2%).

Cushing's syndrome has been reported in infants and adults as a result of prolonged use of topical clobetasol propionate formulations.

Clobetasol is a super-high potency topical corticosteroid; therefore, treatment should be limited to 2 consecutive weeks, and amounts greater than 50 g per week should not be used.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Clobetasol should not be used with occlusive dressings.

**Products**
- **CLOBETASOL BUTYRATE CREAM 0.05% 25 GM TUBE (EUMOVATE®)**
- **CLOBETASOL BUTYRATE OINTMENT 0.05% 25 GM TUBE (EUMOVATE®)**
- **CLOBETASOL PROPIONATE CREAM 0.05% 25 GM TUBE (CLODERM®, DELOR®, DERMOVATE®, MEDODERMONE®)**
- **CLOBETASOL PROPIONATE OINTMENT 0.05% 15-25 GM TUBE (CLODERM®, DELOR®, DERMOVATE®, MEDODERMONE®)**

**DEXAMETHASONE (SKIN)**

**Adverse Effects, Treatment, Withdrawal, and Precautions**
As for corticosteroids in general

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged application to the eye of preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

**Products**
- **DEXAMETHASONE 0.12% + SALICYLIC ACID 2% SCALP LOTION 30 ML BOTTLE (DEXASALYL®, SALIDEX®)**
- **DEXAMETHASONE 0.12% + SALICYLIC ACID 3% OINTMENT 20 GM TUBE (DEXASALYL®)**

**HYDROCORTISONE (SKIN)**

**Mode of action**
Anti-inflammatory, immunosuppressive and antimitotic activity against cutaneous fibroblasts and epidermal cells. They also cause vasoconstriction which has been used to measure their potency.

Useful in a range of skin conditions including insect bite reactions, sunburn and as adjuncts to other treatments.

**Indications**
Inflammatory skin conditions, eg eczema, psoriasis

**Contraindications**
Rosacea
Acne vulgaris
Allergy to corticosteroids or preservatives in vehicle
Ulcerative conditions and/or impaired circulation
Uncontrolled infection in area to be treated

**Specific considerations**
Pregnancy: Use the lowest potency for the shortest time necessary where emollients and other simple measures are inadequate; ADEC category A.

Skin atrophy: increases systemic absorption and skin atrophy; avoid use.

Diabetes: systemic absorption increases blood glucose; avoid extensive use.

Impaired T cell function: systemic absorption results in immunosuppression; avoid extensive use.
Elderly: Skin atrophy makes cutaneous adverse effects more likely.
Children: More susceptible to systemic absorption due to higher surface area/bodyweight ratio.
Hydrocortisone is adequate initial treatment for most children with mild-to-moderate disease. Use stronger preparations for short periods under close supervision.
Consider a corticosteroid-free period of at least 2 weeks after each 2–3 week period of daily use.
Lactation: Safe to use; ensure breast area is free of corticosteroid before nursing.

Adverse effects
Relative potency, patient age, site and extent of disease, preparation type, method of application and length of treatment determine the incidence and severity of adverse effects.
Common: folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, striae, purpura, depigmentation, telangiectasia
Infrequent: allergic contact dermatitis
Rare: hyperaesthesia, subcutaneous tissue atrophy, systemic effects (hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, growth retardation, Cushing's syndrome, cataract)

Dosage
Apply sparingly 1–2 times a day.

Practice points
- use an appropriately potent preparation for the shortest time required to control skin disorder then stop corticosteroid
- therapy can be staged (eg remove precipitating factors and use a moisture care plan, then add topical corticosteroids, sedating antihistamines and tar, in order) with the aim of using the fewest number of treatments to control the disease
- apply sparingly in thin layers by smoothing gently into skin, preferably after bathing
- avoid tolerance by applying corticosteroid on alternate days or instituting medication-free periods (eg 5 days on then 2 days off) during treatment of chronic dermatoses

Nappy dermatitis
- treat with a mild topical corticosteroid initially
- advise parents to use highly absorbent disposable nappies and change nappy frequently; avoid plastic pants because of occlusive effect; nappy free periods should be maximised
- use a protective agent (eg zinc cream)
- often complicated by candidal infection (treat with a topical antifungal).

Products
HYDROCORTISONE ACETATE CREAM 1% (ALFACORT®, HYDROCORT®)
HYDROCORTISONE ACETATE OINTMENT 1% (ALFACORT®)
HYDROCORTISONE BUTYRATE CREAM 0.1% (LOCOID LIPO®, ZONA®)
HYDROCORTISONE BUTYRATE SKIN LOTION 0.1% 100 ML BOTTLE (LOCOID LIPO®)

METHYLPREDNISOLONONE (SKIN)

Mode of action
Anti-inflammatory, immunosuppressive and antimitotic activity against cutaneous fibroblasts and epidermal cells.
They also cause vasoconstriction which has been used to measure their potency.
Useful in a range of skin conditions including insect bite reactions, sunburn and as adjuncts to other treatments.

Indications
Inflammatory skin conditions, eg eczema, psoriasis

Contraindications
Rosacea
Acne vulgaris
Allergy to corticosteroids or preservatives in vehicle
Ulcereative conditions and/or impaired circulation
Uncontrolled infection in area to be treated

Specific considerations
Pregnancy: Use the lowest potency for the shortest time necessary where emollients and other simple measures are inadequate; ADEC category A.
Skin atrophy: increases systemic absorption and skin atrophy; avoid use.
Diabetes: systemic absorption increases blood glucose; avoid extensive use.
Impaired T cell function: systemic absorption results in immunosuppression; avoid extensive use.
Elderly: Skin atrophy makes cutaneous adverse effects more likely.
Children: More susceptible to systemic absorption due to higher surface area/bodyweight ratio.

Hydrocortisone is adequate initial treatment for most children with mild-to-moderate disease. Use stronger preparations for short periods under close supervision.
Consider a corticosteroid-free period of at least 2 weeks after each 2–3 week period of daily use.
Lactation: Safe to use; ensure breast area is free of corticosteroid before nursing.

Adverse effects

Relative potency, patient age, site and extent of disease, preparation type, method of application and length of treatment determine the incidence and severity of adverse effects.
Common: folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, striae, purpura, depigmentation, telangiectasia
Infrequent: allergic contact dermatitis
Rare: hyperaesthesia, subcutaneous tissue atrophy, systemic effects (hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, growth retardation, Cushing’s syndrome, cataract)

Dosage

Apply sparingly once a day.

Practice points

- use an appropriately potent preparation for the shortest time required to control skin disorder then stop corticosteroid
- therapy can be staged (eg remove precipitating factors and use a moisture care plan, then add topical corticosteroids, sedating antihistamines and tar, in order) with the aim of using the fewest number of treatments to control the disease
- apply sparingly in thin layers by smoothing gently into skin, preferably after bathing
- avoid tolerance by applying corticosteroid on alternate days or instituting medication-free periods (eg 5 days on then 2 days off) during treatment of chronic dermatoses

Nappy dermatitis

- treat with a mild topical corticosteroid initially
- advise parents to use highly absorbent disposable nappies and change nappy frequently; avoid plastic pants because of occlusive effect; nappy free periods should be maximised
- use a protective agent (eg zinc cream)
- often complicated by candidal infection (treat with a topical antifungal).

Products

METHYLPREDNISOLON CREAM 1 % (AS OXYPONATE) 20 GM TUBE (ADVANTAN®)
METHYLPREDNISOLON OINTMENT 1 % (AS OXYPONATE) 20 GM TUBE (ADVANTAN®)

MOMETASONE (SKIN)

Mode of action

Anti-inflammatory, immunosuppressive and antimitotic activity against cutaneous fibroblasts and epidermal cells. They also cause vasoconstriction which has been used to measure their potency.
Useful in a range of skin conditions including insect bite reactions, sunburn and as adjuncts to other treatments.

Indications

Inflammatory skin conditions, eg eczema, psoriasis

Contraindications

Rosacea
Acne vulgaris
Allergy to corticosteroids or preservatives in vehicle
Ulcerative conditions and/or impaired circulation
Uncontrolled infection in area to be treated

Specific considerations

Pregnancy: Use the lowest potency for the shortest time necessary where emollients and other simple measures are inadequate. Safety data are lacking; ADEC category B3.
Skin atrophy: increases systemic absorption and skin atrophy; avoid use.
Diabetes: systemic absorption increases blood glucose; avoid extensive use.
Impaired T cell function: systemic absorption results in immunosuppression; avoid extensive use.
Elderly: Skin atrophy makes cutaneous adverse effects more likely.
Children: More susceptible to systemic absorption due to higher surface area/bodyweight ratio.
Hydrocortisone is adequate initial treatment for most children with mild-to-moderate disease. Use stronger preparations for short periods under close supervision.
Consider a corticosteroid-free period of at least 2 weeks after each 2–3 week period of daily use.
Lactation: Safe to use; ensure breast area is free of corticosteroid before nursing.

**Adverse effects**
Relative potency, patient age, site and extent of disease, preparation type, method of application and length of treatment determine the incidence and severity of adverse effects.
Common: folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, striae, purpura, depigmentation, telangiectasia
Infrequent: allergic contact dermatitis
Rare: hyperaesthesia, subcutaneous tissue atrophy, systemic effects (hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, growth retardation, Cushing's syndrome, cataract)

**Dosage**
Apply sparingly once a day.

**Practice points**
- use an appropriately potent preparation for the shortest time required to control skin disorder then stop corticosteroid
- therapy can be staged (eg remove precipitating factors and use a moisture care plan, then add topical corticosteroids, sedating antihistamines and tar, in order) with the aim of using the fewest number of treatments to control the disease
- apply sparingly in thin layers by smoothing gently into skin, preferably after bathing
- avoid tolerance by applying corticosteroid on alternate days or instituting medication-free periods (eg 5 days on then 2 days off) during treatment of chronic dermatoses

Nappy dermatitis
- treat with a mild topical corticosteroid initially
- advise parents to use highly absorbent disposable nappies and change nappy frequently; avoid plastic pants because of occlusive effect; nappy free periods should be maximised
- use a protective agent (eg zinc cream)
- often complicated by candidal infection (treat with a topical antifungal).

**Products**
MOMETASON CREAM 0.1 % 15-30 GM TUBE (ELNA®, ELOCOM®, MESONE®)

**TRIAMCINOLONE (SKIN)**

**Mode of action**
Anti-inflammatory, immunosuppressive and antimitotic activity against cutaneous fibroblasts and epidermal cells. They also cause vasoconstriction which has been used to measure their potency. Useful in a range of skin conditions including insect bite reactions, sunburn and as adjuncts to other treatments.

**Indications**
Inflammatory skin conditions, eg eczema, psoriasis

**Contraindications**
Rosacea
Acne vulgaris
Allergy to corticosteroids or preservatives in vehicle
Ulcerative conditions and/or impaired circulation
Uncontrolled infection in area to be treated

**Specific considerations**
Pregnancy: Use the lowest potency for the shortest time necessary where emollients and other simple measures are inadequate; ADEC category A.
Skin atrophy: increases systemic absorption and skin atrophy; avoid use.
Diabetes: systemic absorption increases blood glucose; avoid extensive use.
Impaired T cell function: systemic absorption results in immunosuppression; avoid extensive use.
Elderly: Skin atrophy makes cutaneous adverse effects more likely.
Children: More susceptible to systemic absorption due to higher surface area/bodyweight ratio.
Hydrocortisone is adequate initial treatment for most children with mild-to-moderate disease. Use stronger preparations for short periods under close supervision.
Consider a corticosteroid-free period of at least 2 weeks after each 2–3 week period of daily use.
Lactation: Safe to use; ensure breast area is free of corticosteroid before nursing.

**Adverse effects**
Relative potency, patient age, site and extent of disease, preparation type, method of application and length of treatment determine the incidence and severity of adverse effects.
Common: folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, striae, purpura, depigmentation, telangiectasia
Infrequent: allergic contact dermatitis
Rare: hyperaesthesia, subcutaneous tissue atrophy, systemic effects (hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, growth retardation, Cushing’s syndrome, cataract)

**Dosage**
Apply sparingly 1–2 times day.

**Practice points**
- Use an appropriately potent preparation for the shortest time required to control skin disorder then stop corticosteroid
- Therapy can be staged (eg remove precipitating factors and use a moisture care plan, then add topical corticosteroids, sedating antihistamines and tar, in order) with the aim of using the fewest number of treatments to control the disease
- Apply sparingly in thin layers by smoothing gently into skin, preferably after bathing
- Avoid tolerance by applying corticosteroid on alternate days or instituting medication-free periods (eg 5 days on then 2 days off) during treatment of chronic dermatoses

**Nappy dermatitis**
- Treat with a mild topical corticosteroid initially
- Advise parents to use highly absorbent disposable nappies and change nappy frequently; avoid plastic pants because of occlusive effect; nappy free periods should be maximised
- Use a protective agent (eg zinc cream)
- Often complicated by candidal infection (treat with a topical antifungal).

**Products**
**TRIAMCINOLONE OINTMENT 0.1 % (KENACIN A®)**

**13.01.02 Coal Tar (Skin)**

**COAL TAR (SKIN)**

**Mode of action**
Exact mechanism unknown. Tars suppress DNA synthesis, reduce epidermal thickness, are antipruritic and may be weakly antiseptic.

**Indications**
Eczema, particularly chronic or lichenified eczema
Seborrhoeic dermatitis
Stable chronic plaque psoriasis
Dandruff

**Contraindications**
Inflamed, broken skin
Infection
Previous allergic reaction to coal tar
Conditions characterised by photosensitivity, eg lupus erythematosus, polymorphic light eruption (coal tars contraindicated because of photosensitising action)
Unstable psoriasis

**Specific considerations**
Treatment with photosensitising medications: increases risk of phototoxic reactions; avoid combinations.
Children: Safety and efficacy of coal tar preparations have not been established. Should not be used in children <2 years, except under the direction and supervision of a dermatologist.
Pregnancy: Data lacking, unlikely to be a concern.
Lactation: Safe to use.

**Adverse effects**
Common: mild stinging
Rare: folliculitis, irritant reactions, allergic reactions, photosensitivity, acneiform eruptions
Others: staining of skin, hair (especially in patients with fair, bleached or grey hair) and clothing
Carcinogenicity: Conflicting evidence.

**Dosage**
Shampoo, once a week to once a day.
Cream, lotion, 2–4 times a day.
Gel, 2–4 times a day.
Medicated bar, use as soap.

Dose equivalence
Extemporaneous products, 1% crude coal tar is equivalent to 5% coal tar solution.

**Administration instructions**
Shampoo, apply to wet hair, massage vigorously into scalp and leave for 3–5 minutes; rinse thoroughly; repeat application and rinse.
Cream, gel, apply enough to cover affected area and rub in gently.

**Patient counselling**
Do not use near eyes.
May stain skin, hair and clothes.
Avoid exposure to direct sunlight or sunlamps for at least 24 hours after application. Completely remove coal tar preparations before exposure to sunlight.

**Practice points**
- may be used alone in treatment of psoriasis, or combined with dithranol and/or ultraviolet light
- use low concentrations (0.5–1%) on face, flexures and genitals to reduce potential for irritation
- patient acceptance may be poor due to the messiness, smell and staining properties of some preparations
- salicylic acid, sulfur and allantoin have keratolytic properties and may be used in combination with coal tar in the treatment of psoriasis, seborrhoeic dermatitis and dandruff
- pyrithione zinc has bacteriostatic and fungistatic properties and is available with coal tar for the treatment of seborrhoeic dermatitis and dandruff

**Products**
**COAL TAR SHAMPOO®**

**13.01.03 Other drugs for eczema**

**PIMECROLIMUS (SKIN)**

**Mode of action**
Anti-inflammatory, but precise mechanism unknown. Inhibits calcineurin thus blocking T-cell activation, prevents release of inflammatory mediators from mast cells.

**Indications**
Short term treatment of active mild-to-moderate eczema in children >3 months and adults

**Contraindications**
Cutaneous viral infection

**Specific considerations**
Immunosuppression, skin cancer: avoid use, theoretical risk of toxicity.
Bacterial or fungal skin infections: treat area before starting pimecrolimus.
Pregnancy: Limited data; ADEC category B3.
Lactation: No data, seek specialist advice.

**Adverse effects**
Common: local irritation, burning sensation, itch, erythema, skin infections
Infrequent: local rash, aggravation of eczema, herpes simplex dermatitis, impetigo

**Dosage**
Apply twice a day in a thin film to affected areas.

**Administration instructions**
Apply to clean, dry skin.

**Patient counselling**
Avoid contact with eyes, mouth and other mucous surfaces.
Avoid exposure to sun, use an effective sunscreen.

**Practice points**
• due to concerns about possible increased incidence of adverse effects (upper respiratory tract infections, otitis media, diarrhoea, asthma, irritability), pimecrolimus is not approved for use in children <2 years in the USA or the UK
• stop treatment if condition deteriorates or there is no noticeable improvement after 6 weeks
• if irritation occurs, apply less frequently; if it persists or is severe, stop treatment
• data comparing pimecrolimus with topical corticosteroids is limited; it is much more expensive than topical corticosteroid treatment and benefit over such agents has not been confirmed
• safety of long term use has not been clearly established

Products
PIMECROLIMUS CREAM 1%  30 GM TUBE (ELIDEL®)

TACROLIMUS
Mode of Action
The mechanism of action of tacrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). Tacrolimus also inhibits the transcription for genes which encode IL-3, IL-4, IL-5, GM-CSF, and TNF-(alpha), all of which are involved in the early stages of T-cell activation. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils, and to downregulate the expression of Fc[egr]RI on Langerhans cells.

Indication and usage
Tacrolimus Ointment 0.1% for adults, is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate to severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of, alternative, conventional therapies.

Contraindications
Contraindicated in patients with a history of hypersensitivity to tacrolimus or any other component of the preparation.

Precautions
General
Studies have not evaluated the safety and efficacy in the treatment of clinically infected atopic dermatitis. Before commencing treatment, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi’s varicelliform eruption), treatment may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these infections, the balance of risks and benefits associated with Tacrolimus Ointment use should be evaluated. In clinical studies, 33 cases of lymphadenopathy (0.8%) were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. Of these 33 cases, the majority had either a clear etiology or were known to resolve. Transplant patients receiving immunosuppressive regimens (e.g., systemic tacrolimus) are at increased risk for developing lymphoma; therefore, patients who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation should be considered.

Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans, Tacrolimus Ointment shortened the time to skin tumor formation in an animal photocarcinogenicity study. Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

The use of Tacrolimus Ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of application and typically improve as the lesions of atopic dermatitis heal. With Tacrolimus Ointment 0.1%, 90% of the skin burning events had a duration between 2 minutes and 3 hours (median 15 minutes). Ninety percent of the pruritus events had a duration between 3 minutes and 10 hours (median 20 minutes).

Patients counseling
Patients using Tacrolimus Ointment should receive the following information and instructions:
Patients should use Tacrolimus Ointment as directed by the physician. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UV A/B treatment) while using Tacrolimus Ointment.

Patients should not use this medication for any disorder other than that for which it was prescribed. Patients should report any signs of adverse reactions to their physician.

**Pregnancy:**
Teratogenic Effects: Pregnancy Category C

**Pediatric Use:** Tacrolimus Ointment 0.03% may be used in pediatric patients 2 years of age and older. Two phase 3 pediatric studies were conducted involving 606 patients 2-15 years of age: one 12-week randomized vehicle-controlled study and one open-label, 1 year, long-term safety study. Three hundred and thirty (330) of these patients were 2 to 6 years of age.

**Geriatric Use:** Twenty-five (25) patients >/= 65 years old received Tacrolimus Ointment in phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

**Adverse effects**
No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study. In three randomized vehicle-controlled studies and two long-term safety studies, 655 and 571 patients respectively, were treated with Tacrolimus Ointment.

The following table depicts the adjusted incidence of adverse events pooled across the 3 identically designed 12 week studies for patients in vehicle, Tacrolimus Ointment 0.03%, and Tacrolimus Ointment 0.1% treatment groups, and the unadjusted incidence of adverse events in two one year long-term safety studies, regardless of relationship to study drug.

**Dosage and administration**
Adults: Apply a thin layer to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis.

Pediatric: Apply a thin layer of Tacrolimus Ointment 0.03% to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis.

**Products**
- **TACROLIMUS OINTMENT 0.1 % (PROGRAF®, PROTOPEC®)**
- **TACROLIMUS OINTMENT 0.03 % (PROTOPEC®)**

### 13.02 DRUGS FOR ACNE

**ACNE**

Acne vulgaris is a common skin disease caused by increased sebum production, abnormal follicular keratinization, proliferation of Propionibacterium acnes and inflammation. Management is directed at these factors.

Mild acne is characterised by comedones with some papules and pustules. In moderate acne, the papules and pustules are more widespread and there may be mild scarring. Severe acne is characterised by nodular abscesses and cysts in addition to widespread papules and pustules and may lead to extensive scarring.

**Rationale for drug use**
- Improve complexion, reduce the number of lesions.
- Prevent scarring.
- Limit disease duration.
- Reduce psychological stress (depression and low self esteem) related to acne.

**Before starting treatment**
Hormonal evaluation is indicated if hirsutism, alopecia or menstrual irregularities are present.

**When to start treatment**
Start early to prevent scarring; tailor treatment according to severity.

**Choice of topical treatment**
Retinoids, benzoyl peroxide or azelaic acid are used as first line treatments in mild acne and with oral antibacterials in moderate acne. Apply to entire affected area and not just to individual lesions.

**Retinoids**
Tretinoin, adapalene or isotretinoin (skin) are the treatment of choice for comedonal acne. May be used with other...
topical and oral (antibacterial or hormonal) treatments. Irritation may increase with use of >1 topical treatment. Do not use during pregnancy because of potential risk of teratogenicity.

**Benzoyl peroxide and azelaic acid**

Benzoyl peroxide has antibacterial activity and is mildly comedolytic; first line treatment in comedonal and mild inflammatory acne. May be used with topical or oral antibacterials; can be used on alternate days with topical retinoids; some patients can tolerate same day applications of benzoyl peroxide and a topical retinoid. Azelaic acid has antibacterial activity and is comedolytic; it is a less irritating alternative to benzoyl peroxide in mild inflammatory acne. Should be used cautiously in patients with dark complexions (may cause hypopigmentation). Hypopigmentation effects may be useful if acne has caused hyperpigmented scars.

**Antibacterials**

Clindamycin and erythromycin (skin) may also have indirect effects on comedogenesis; clinical efficacy is similar. Development of antibacterial resistance by skin flora is an increasing problem. Add to topical retinoid, benzoyl peroxide or azelaic acid in mild acne after 6–8 weeks if there is inadequate response.

**Choice of oral treatment**

In addition to topical retinoid, benzoyl peroxide or azelaic acid in mild acne after 6–8 weeks if there is inadequate response.

**Choice of oral treatment**

Includes antibacterials, hormonal treatments and isotretinoin.

**Antibacterials**

Are useful in treatment of moderate acne; doxycycline and tetracycline are the drugs of choice. Minocycline, although widely used, is less well tolerated and has been associated more commonly with CNS adverse effects, including benign intracranial hypertension; may also cause hepatitis, a lupus-like syndrome and altered skin pigmentation. Erythromycin may be used if tetracyclines are not tolerated or are contraindicated. Antibacterials may be used with topical agents. Improvement may not begin until after 4–8 weeks of treatment. Treatment should be changed if there is no response after 3 months. They must be taken for at least 3–6 months to obtain a good response; in some patients longer term treatment may be necessary.

**Hormonal treatments**

Are limited to treatment of acne in females; they reduce sebum secretion which is under androgen control. Several months of treatment are usually required before benefit occurs; prolonged treatment is needed to maintain improvement. Oestrogens suppress ovarian androgen production; usually prescribed as combined oral contraceptive (COC). Beneficial effect is most apparent at doses of 50 micrograms or more of ethinyloestradiol (or equivalent), but even a low dose COC (particularly one that contains a less androgenic progestogen, such as desogestrel) may be effective. Consider adding to topical retinoid, benzoyl peroxide or azelaic acid in moderate acne either in addition to, or instead of, an oral antibacterial. Cyproterone is an antiandrogen and is used with ethinyloestradiol for the control of severe acne refractory to prolonged oral antibacterial treatment, see Cyproterone with ethinyloestradiol. Higher doses of cyproterone are occasionally recommended by specialists, particularly if seborrhoea or hirsutism are also present. Spironolactone has potent antiandrogen activity and has been used by specialists to treat severe acne.

**Isotretinoin**

Acts primarily by reducing sebum secretion; used in severe acne or in moderate acne unresponsive to conventional treatment. Known teratogen; pregnancy and blood donation should be avoided during treatment and for at least 1 month after stopping treatment.

**Other drug treatments**

Include abrasive agents, eg aluminium oxide; degreasing agents, eg triclosan; and preparations containing sulfur, salicylic acid, resorcinol and allantoin. Although widely used, effectiveness is questionable. Exfoliants may limit tolerance to other more effective agents and have no effect on sebaceous gland activity.

**Special cases**

Acne conglobata, acne fulminans and pyoderma faciale are severe forms of inflammatory acne that require urgent specialist referral for treatment with isotretinoin and oral corticosteroids.

**Patient counselling**

Wash affected areas gently; avoid vigorous scrubbing and abrasive cleansers, which may cause more inflammation and make acne worse. Avoid using toners and oil-based moisturisers. Do not squeeze or pick the acne lesions (pimples). Eat a healthy balanced diet; there is no relationship between particular foods and acne.

**Practice points**

- consider using 2 or 3 agents that act in different ways
• avoid systemic antibiotics if a topical medication will suffice
• do not switch or rotate antibiotics in patients who are responding to therapy (response indicates efficacy and changing antibiotics may promote resistance)

13.02.01 Keratolytics

BENZOYL PEROXIDE

Mode of action
Antibacterial action probably due to oxidising effect; mild keratolytic properties.

Indications
Acne vulgaris

Contraindications
Allergy to benzoil peroxide

Specific considerations
Inflamed or broken skin: increases systemic absorption.
Children: Safety and efficacy are not established in children, but problems are not expected.
Pregnancy: Safe to use.
Lactation: Safe to use.

Adverse effects
Common: skin dryness or peeling, feeling of warmth, mild stinging or erythema
Rare: allergic contact dermatitis

Dosage
Apply once or twice a day: begin treatment with 2.5% or 5% product, then change to 10% strength after 3–4 weeks, or sooner if tolerance to the lower strengths develops.

Administration instructions
Before applying, wash affected area with mild soap or soap substitute and warm water; gently pat dry. Apply enough medication to cover affected area and rub in gently.

Patient counselling
Avoid contact with eyes, mouth and other mucous membranes.
Avoid contact with hair and coloured fabric as bleaching or discoloration may result.

Practice points
• cumulative irritant or drying effects with other topical anti-acne preparations; combinations may be used if tolerated by patient
• benzoyl peroxide inactivates topical tretinoin; apply 12–24 hours apart
• effective first line treatment for mild acne when used alone; may be used on alternate days with topical retinoids and with topical or oral antibacterials in more severe acne; however, irritation may be a problem with such combinations
• if irritation occurs, apply less frequently or use a lower strength preparation; if it persists, is severe or is thought to be due to allergy, stop treatment

Products
BENZOYL PEROXIDE GEL 5 % 40-60 GM TUBE (BENOXYPHIL®, PANOXYL®)

13.02.02 Antibacterials

CLINDAMYCIN (SKIN)

Mode of action
Lincosamide antibacterial; inhibits growth of Propionibacterium acnes.

Indications
Acne vulgaris, mild-to-moderate

Specific considerations
History of antibacterial-associated colitis, regional enteritis or ulcerative colitis: small risk of systemic adverse effects, eg colitis, following topical application.
Pregnancy: Safe to use; ADEC category A.
Lactation: Safe to use; low topical absorption.

Drug interactions
See Clindamycin
Adverse effects
Common: dry, scaly or peeling skin
Infrequent: contact dermatitis
Rare: pseudomembranous colitis
Dosage
Apply twice a day. Application to the entire face is equivalent to approximately 2 mL of liquid or lotion.
Administration instructions
Before applying, wash affected areas with mild soap or soap substitute and warm water; rinse and pat dry.
Patient counselling
Do not use near heat, open flame or if smoking (products contain alcohol).
Avoid contact with eyes, mouth and other mucous membranes.
Stop use and tell your doctor if GI symptoms such as diarrhoea occur.
Practice points
- noticeable improvement is usually seen after about 6 weeks in most patients; however, 8–12 weeks of treatment may be required before maximum benefit is seen
- avoid combination with topical erythromycin preparation (antagonistic mode of action)
- cumulative irritant or drying effects may occur if used with other topical anti-acne preparations; combinations may be used if tolerated by patient
Products
CLINDAMYCIN SOLUTION 1 % 30 ML BOTTLE (CLINADERM®, CLINDOX®, CLINDACIN-T®, DALACIN-T®, DERMOVATE®, LINDASOL®)
ERYTHROMYCIN (SKIN)
Mode of action
Macrolide antibacterial; inhibits growth of Propionibacterium acnes.
Indications
Marketed: Acne vulgaris, mild-to-moderate
Accepted: Minor bacterial skin infections
Specific considerations
Pregnancy: Safe to use; ADEC category A.
Lactation: Safe to use.
Adverse effects
Common: dry or scaly skin, itch, stinging or burning feeling
Infrequent: desquamation, erythema
Dosage
Apply twice a day in a thin film to affected areas.
Administration instructions
Before application, wash affected area with a mild soap or soap substitute and warm water; rinse thoroughly and pat dry.
Patient counselling
Avoid contact with eyes, mouth and other mucous surfaces.
Do not use near heat or open flame or if smoking (contains alcohol).
Practice points
- noticeable improvement may be seen in 3–4 weeks; however, 8–12 weeks of treatment may be required before maximum benefit is seen
- if irritation occurs, apply less frequently; if it persists or is severe, stop treatment
- combination treatment with benzoyl peroxide and topical erythromycin may prevent resistance; use with caution due to cumulative irritant effects
- avoid combination with topical clindamycin preparation (antagonistic mode of action)
- cumulative irritant or drying effects may occur if used with other topical anti-acne preparations; combinations may be used if tolerated by patient
Products
ERYTHROMYCIN LOTION 40 MG/ML + ZINC ACETATE 12 MG/ML 30 GM BOTTLE (ZINYRET®)
ERYTHROMYCIN SOLUTION 2 % 25 ML BOTTLE (AKNE-MYCIN®, PHILAMYCIN®, STIEMYCIN®)
13.02.03 Retinoids (Oral)

**ACITRETIN (ORAL)**

**Mode of action**
Reverses the epidermal proliferation and increased keratinization seen in hyperkeratotic disorders.

**Indications**
- Cystic acne, severe (isotretinoin)
- Psoriasis, severe (acitretin)
- Keratinization disorders, severe (acitretin)

**Contraindications**
- Pregnancy
- Breastfeeding
- Hepatic impairment

**Specific considerations**
- Renal impairment: Avoid in endstage renal disease; use lower doses in patients with renal impairment.
- Children: Because of the unknown effects of acitretin on growth and skeletal development and the risk of premature epiphyseal closure, acitretin should be used in people <18 years only in: life-threatening circumstances where other treatment cannot be used or is ineffective (eg widespread pustular psoriasis), severe disorders for which there is no alternative treatment.
- Growth parameters and bone development must be closely monitored by regular measurement and x-ray in all children on long term treatment.
- Pregnancy: Contraindicated; ADEC category X.
- Acitretin is the active metabolite of etretinate which has been reported to cause major human fetal abnormalities if administered during pregnancy. Acitretin may also be converted to etretinate in the body. Alcohol intake may increase this conversion.
- Breastfeeding: Contraindicated.
- Hyperlipidaemia, obesity, excessive alcohol intake, diabetes: oral retinoids are associated with increased risk of hypertriglyceridaemia and cardiovascular disease; avoid use or monitor carefully because of further risk of triglyceride elevation.
- Women of child-bearing age
  - Treatment with tetracyclines: increases risk of benign intracranial hypertension; avoid combination (contraindicated by manufacturer).
  - Treatment with topical retinoids: increases risk of adverse effects; avoid combination.
  - Treatment with photosensitising medications: increases risk of phototoxic reactions; avoid combination.
  - Elderly: Arthralgias are more common; monitor carefully.
- Children: Risk of premature epiphyseal closure; seek specialist advice.
- Pregnancy: The elimination half-life for isotretinoin is 20 hours and for acitretin, 50 hours. However, due to possible conversion of acitretin to etretinate, which has an elimination half-life of 120 days or more, the recommended contraception period is significantly longer with acitretin.
- Breastfeeding: Contraindicated.

**Adverse effects**
- Common: nail fragility, sticky skin, taste disturbance, blurred vision and impaired night vision
- Infrequent: vertigo, somnolence
- Rare: granulomatous lesions, bullous eruptions
- Most patients experience adverse effects which generally resemble excess vitamin A intake.

**Dosage**
- **Adult**
  - Initially, 25–30 mg once a day for 2–4 weeks.
  - Maintenance, based on clinical efficacy and tolerance; generally 25–50 mg once a day for a further 6–8 weeks.
  - Longer courses using lower doses have been used.
  - Treatment may be stopped if lesions have resolved sufficiently.
- **Child**: 0.5–1 mg/kg daily; maximum daily dose 35 mg.

**Patient counselling**
- Do not donate blood during, and for at least 2 years after, treatment.
- Female patients, it is important that you use adequate contraception before, during and for 2 years after, treatment, because birth defects have occurred during this time.
- Avoid alcohol during, and for 2 months after, treatment.
Psoriasis, sometimes psoriasis becomes worse for a short time after starting treatment.

**Practice points**
- confirm a negative pregnancy test in the 2 weeks before starting treatment, then start on the second or third day of the next normal menstrual period
- ensure effective contraception before, during and after treatment; an oestrogen–progestogen combined pill is the contraceptive method of choice; another method of contraception may be used as well, eg condoms or diaphragm, to minimise pregnancy risk
- complete blood count, biochemical profile, liver function and fasting blood lipids should be measured at baseline, after the first month of treatment and then as required
- blood glucose should be monitored throughout treatment in patients who either have, or are predisposed to, type 1 diabetes
- consider radiological evaluation for skeletal hyperostosis in patients receiving long term treatment (>1 year)

**Products**
- ACITRETIN CAPS 10 MG (NEOTIGASON®)
- ACITRETIN CAPS 25 MG (NEOTIGASON®)

**ISOTRETINOIN (ORAL)**

**Mode of action**
Modulates cell proliferation and differentiation. Reduces sebum excretion, Propionibacterium acnes numbers, inflammation and cyst formation.

**Indications**
Marketed: Cystic acne, severe
Accepted: Neoplastic disorders, eg squamous cell carcinoma
Disorders of keratinization

**Contraindications**
- Pregnancy
- Lactation
- Hepatic impairment

**Specific considerations**
- Pregnancy
- Contraindicated; ADEC category X.
- Lactation

**Contraindicated.**
Hyperlipidaemia, obesity, excessive alcohol intake, diabetes: oral retinoids are associated with increased risk of hypertriglyceridaemia and cardiovascular disease; avoid use or monitor carefully because of further risk of triglyceride elevation.
Women of child-bearing age.
Treatment with tetracyclines: increases risk of benign intracranial hypertension; avoid combination (contraindicated by manufacturer).
Treatment with topical retinoids: increases risk of adverse effects; avoid combination.
Treatment with photosensitising medications: increases risk of phototoxic reactions; avoid combination.
Elderly: Arthralgias are more common; monitor carefully.
Children: Risk of premature epiphyseal closure; seek specialist advice.
Pregnancy: ISOTRETINOIN is contraindicated; and is teratogenic; ADEC category X. Women should use effective contraceptive measures for 1 month before starting treatment, during treatment, for 1 month after stopping isotretinoin and for at least 2 years after stopping acitretin. Should women conceive during this period there is a high risk of birth defects.
Lactation: Contraindicated.

**Adverse effects**
Common: dryness of skin, lips and mucous membranes; cheilitis, mild acne flare, conjunctivitis and epistaxis, reduced tolerance to contact lenses, raised blood glucose (diabetics), photosensitivity
Infrequent: depression, hair thinning, myalgias, arthralgias, fatigue, headache, severe acne flare, menstrual disturbances, raised liver enzymes
Rare: corneal opacities, cataracts, papilloedema, decreased night vision, optic neuritis, benign intracranial hypertension, skeletal hyperostosis, inflammatory bowel disease, hepatitis
Hyperlipidaemia
Increases in serum triglycerides and total cholesterol and decreases in high density lipoproteins, may occur; these effects are dose-dependent, occur early during treatment and are usually reversible within a few weeks of stopping therapy.

**Dosage**
Initially, up to 0.5 mg/kg each day as a single dose or in 2 divided doses. Dosage may be increased to 1 mg/kg after 4 weeks according to response and tolerance. Treatment should be continued until total cumulative dose is 100 mg/kg for moderate acne, or 150 mg/kg for severe acne. A treatment course is usually 4–6 months.

Patients with acne primarily on the body instead of the face may require a total cumulative dose of up to 150 mg/kg.

**Patient counselling**
Hair removal by waxing may tear your skin during, and for 2 months after stopping, treatment because of fragile skin. Do not give blood during treatment or for 1 month after stopping treatment. Use white soft paraffin, eg Vaseline®, to treat dry lips; use lubricating eye drops to treat eye irritation. Tell your doctor if you are unable to manage dry skin, dry lips or dry eyes, or if during the initial treatment period your contact lenses become uncomfortable. Report promptly any nausea, headaches or visual changes (including impaired night vision or blurring) to your doctor. Tell your doctor if you notice a change in your moods. Avoid taking vitamin A supplements. Protect skin from sunlight with protective clothing or sunscreen. Broad spectrum sunscreen, at least factor 15+, and containing a physical barrier (eg titanium dioxide or zinc oxide) is recommended. Avoid sunlamps and tanning beds. Do not share medication with others.

**Practice points**
- a mild flare of acne commonly occurs after 2–4 weeks of treatment, but improves after 1–2 months of continued treatment; severe flares occur infrequently
- most patients remain disease-free after a single course or have long remissions; approximately 10% of patients relapse; repeated courses of isotretinoin are not usually recommended unless recurrence is severe
- allow at least 2 months after completing a course to see whether further treatment is necessary, as improvement may continue for several months after stopping
- use of isotretinoin with antibacterials and antiandrogens does not markedly improve efficacy; if concomitant antibacterial treatment is contemplated, erythromycin is preferred, as use of isotretinoin with tetracyclines can increase the risk of benign intracranial hypertension

**Products**
- ISOTRETINOIN CAPS 10 MG (ROACCUtANE®)
- ISOTRETINOIN CAPS 20 MG (ROACCUtANE®)

### 13.02.04 Retinoids (Skin)

**ADAPALENE**

**Mode of action**
Modulate cell proliferation and differentiation; decrease new comedone formation and inflammatory lesions.

**Indications**
Acne vulgaris, especially early comedonal acne, although may be used adjunctively in the management of comedones associated with inflammatory acne

**Contraindications**
- Allergy to topical retinoids
- Pregnancy
- Sunburn
- Unprotected sun exposure

**Specific considerations**
- Children: Contraindicated in neonates; may be used in young children with comedonal acne.
- Eczema: severe irritation to eczematous skin may occur; use with caution.
- Women of child-bearing age.
- Treatment with oral retinoids: increases risk of adverse effects; avoid combination.
- Treatment with photosensitising medications: increases risk of phototoxic reactions; avoid combination.
- Pregnancy: Contraindicated. Although absorption via skin is minimal, in view of teratogenicity of systemic retinoids,
Topical retinoids should not be used in pregnancy. ADEC category D.

**Lactation:** No data available but unlikely to be a concern.

**Adverse effects**
- Common: erythema, peeling, irritation
- Infrequent: pigmentation changes, photoirritation
- Rare: allergic contact dermatitis

**Dosage**
Apply once a day at bedtime.

**Patient counselling**
Before applying, wash with mild soap or soap substitute and warm water; rinse and gently pat dry; wait 20–30 minutes for complete drying of skin to occur. Apply enough to cover affected areas and rub in gently.

Do not apply to eyes, lips or in nostrils.

Protect treated areas from sunlight with protective clothing or sunscreen. Use broad spectrum sunscreen, at least factor 15+ (30+ is preferable), containing a physical agent (e.g., titanium dioxide). Avoid sunlamps and tanning beds. Cosmetics may be used but skin must be washed thoroughly before applying medication.

**Practice points**
- Cumulative irritant or drying effects may occur with other topical anti-acne preparations; combinations may be used if tolerated by patient
- Confirm a negative pregnancy test in the 2 weeks before starting treatment, then start treatment on the second or third day of the next normal menstrual period
- During early weeks of treatment, an apparent flare of acne may occur; this is due to actions on deep lesions and is not a reason to stop treatment; benefit does not generally become evident for some weeks or even months
- If patients have been using keratolytics, allow sufficient time for their effects to subside before initiating treatment with topical retinoids
- Adverse effects may decrease with time and can be minimised by using a moisturiser
- Excessive application does not increase therapeutic effect and may produce marked inflammation
- If severe erythema, oedema, blistering or crusting occurs, apply less frequently or stop until skin integrity is restored

**Products**
- **ADAPALENE GEL 0.1 % 30 GM (DIFFERIN GEL®)**

**ISOTRETINOIN (SKIN)**

**Mode of action**
Modulate cell proliferation and differentiation; decrease new comedone formation and inflammatory lesions.

**Indications**
- Acne vulgaris, especially comedonal acne, although may be used adjunctively in the management of comedones associated with inflammatory acne
- Acne vulgaris, especially comedonal acne, although may be used adjunctively in the management of associated comedones in inflammatory acne

**Contraindications**
- Allergy to topical retinoids
- Pregnancy
- Sunburn
- Unprotected sun exposure

**Specific considerations**
- Children: Contraindicated in neonates; may be used in young children with comedonal acne.
- Eczema: severe irritation to eczematous skin may occur; use with caution.
- Women of child-bearing age.
- Treatment with oral retinoids: increases risk of adverse effects; avoid combination.
- Treatment with photosensitizing medications: increases risk of phototoxic reactions; avoid combination.
- Pregnancy: Contraindicated. Although absorption via skin is minimal, in view of teratogenicity of systemic retinoids, topical retinoids should not be used in pregnancy. ADEC category D.
- Lactation: No data available but unlikely to be a concern.

**Adverse effects**
- Common: erythema, peeling, irritation
Infrequent: pigmentation changes, photoirritation
Rare: allergic contact dermatitis

Dosage
Apply once a day at bedtime.

Patient counselling
Before applying, wash with mild soap or soap substitute and warm water; rinse and gently pat dry; wait 20–30 minutes for complete drying of skin to occur. Apply enough to cover affected areas and rub in gently.
Do not apply to eyes, lips or in nostrils.
Protect treated areas from sunlight with protective clothing or sunscreen. Use broad spectrum sunscreen, at least factor 15+ (30+ is preferable), containing a physical agent (eg titanium dioxide). Avoid sunlamps and tanning beds. Cosmetics may be used but skin must be washed thoroughly before applying medication.

Practice points
• cumulative irritant or drying effects may occur with other topical anti-acne preparations; combinations may be used if tolerated by patient
• confirm a negative pregnancy test in the 2 weeks before starting treatment, then start treatment on the second or third day of the next normal menstrual period
• during early weeks of treatment, an apparent flare of acne may occur; this is due to actions on deep lesions and is not a reason to stop treatment; benefit does not generally become evident for some weeks or even months
• if patients have been using keratolytics, allow sufficient time for their effects to subside before initiating treatment with topical retinoids
• adverse effects may decrease with time and can be minimised by using a moisturiser
• excessive application does not increase therapeutic effect and may produce marked inflammation
• if severe erythema, oedema, blistering or crusting occurs, apply less frequently or stop until skin integrity is restored

Products
ISOTRETINION GEL 0.05 % + ERYTHROMYCIN 2 % 30 GM TUBE (ISOTREXIN®)

TRETINOIN (SKIN)

Mode of action
Modulate cell proliferation and differentiation; decrease new comedone formation and inflammatory lesions.

Indications
Marketed: Acne vulgaris, especially comedonal acne, although may be used adjunctively in the management of comedones associated with inflammatory acne
Accepted: Photoageing
Acne vulgaris, especially comedonal acne, although may be used adjunctively in the management of associated comedones in inflammatory acne

Contraindications
Allergy to topical retinoids
Pregnancy
Sunburn
Unprotected sun exposure

Specific considerations
Children: Contraindicated in neonates; may be used in young children with comedonal acne.
Eczema: severe irritation to eczematous skin may occur; use with caution.
Women of child-bearing age.
Treatment with oral retinoids: increases risk of adverse effects; avoid combination.
Treatment with photosensitising medications: increases risk of phototoxic reactions; avoid combination.
Pregnancy: Contraindicated. Although absorption via skin is minimal, in view of teratogenicity of systemic retinoids, topical retinoids should not be used in pregnancy. ADEC category D.
Lactation: No data available but unlikely to be a concern.

Adverse effects
Common: erythema, peeling, irritation
Infrequent: pigmentation changes, photoirritation
Rare: allergic contact dermatitis

Dosage
Apply once a day at bedtime.

**Patient counselling**
Before applying, wash with mild soap or soap substitute and warm water; rinse and gently pat dry; wait 20–30 minutes for complete drying of skin to occur. Apply enough to cover affected areas and rub in gently. Do not apply to eyes, lips or in nostrils. Protect treated areas from sunlight with protective clothing or sunscreen. Use broad spectrum sunscreen, at least factor 15+ (30+ is preferable), containing a physical agent (eg titanium dioxide). Avoid sunlamps and tanning beds. Cosmetics may be used but skin must be washed thoroughly before applying medication.

**Practice points**
- start with the lowest strength cream or gel
- benefit may be noticed after 2–3 weeks, but >6 weeks treatment is usually required
- there may be a symptomatic flare in the first 4–6 weeks of treatment
- after achieving satisfactory response, it may be possible to maintain efficacy with less frequent application
- tretinoin and benzoyl peroxide can be applied with a 12–24 hour interval between applications
- topical tretinoin may increase the systemic absorption of topical minoxidil; avoid applying to same area of skin

**Products**
TRETINOIN GEL 0.025 % 30 GM TUBE (OPTIMAL®, RETIN-A®)

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### 13.03 DRUGS FOR FUNGAL AND YEAST INFECTIONS

#### TINEA
Tinea is a superficial fungal infection of the skin, hair or nails caused by dermatophytes. It is classified according to the area affected, eg scalp and hair (tinea capitis), trunk (tinea corporis, ringworm), groin (tinea cruris) and foot (tinea pedis, athlete’s foot). Infection involving the nail (tinea unguium) is discussed in Nail infections.

**Before starting treatment**
Skin scrapings from edge of lesion should be taken for microscopy and culture. Confirmation of fungal infection is warranted as the clinical picture may be very similar to non-fungal conditions (exclude discoid eczema when ringworm-like lesions are present; this is a common misdiagnosis).

**When to start treatment**
Obvious clinical picture or positive microscopy result; it is not necessary to wait for culture results.

**Drug choice**

**Topical treatment**
Mild localised skin infections usually respond to topical treatments, including azoles, terbinafine and tolnaftate. Topical treatment is not usually successful for infections involving the nails and hair. Hyperkeratotic lesions also respond poorly.
Azoled (eg clotrimazole, miconazole) are the treatment of choice; fungistatic; available as cream, lotion, solution, spray and powder; well tolerated.
Terbinafine is more expensive but produces a more rapid response than azoles; fungicidal; available as gel and cream. Tolnaftate may irritate skin; less effective than azoles and terbinafine; available as cream, solution, ointment, powder and spray.
Miscellaneous agents such as benzoic acid with salicylic acid (Whitfield's ointment), undecanoic acid salts, selenium sulfide and crystal violet are less effective than azoles, terbinafine and tolnaftate.

**Systemic treatment**
Griseofulvin, itraconazole or terbinafine are used for tinea capitis, extensive infection, infections in heavily keratinised areas, eg palms and soles, and disseminated disease. They may also be used for tinea pedis, tinea corporis and tinea cruris when there is poor response to topical therapy. Fluconazole may be used but is more commonly reserved for candidal infection.
Griseofulvin has a narrow spectrum of activity confined largely to dermatophytes, so accurate diagnosis is essential. As tissue concentration drops quickly after stopping, it should be continued until condition is cured (typically several weeks or months).

**Other drug treatment**
Drying agents and/or antibacterial agents (such as solution of Condy's crystals or Burow's solution) may be needed for severe forms of interdigital infection.
Saline compresses/drying agents and sometimes topical corticosteroids may be necessary for acute vesicular tinea.
Treatment endpoints
Continue topical treatment for 2 weeks after clinical signs resolve. Continue oral treatment until mycological and clinical cures are obtained.

Practice points
- good personal hygiene is an important adjunct to antifungal treatment, eg drying between toes, using a separate towel for infected area, wearing thongs in public showers and change rooms, changing socks (preferably cotton) daily, avoiding sharing combs, hats and towels
- discard old shoes that may have a high density of fungal spores
- creams are generally preferred; lotions or sprays may be applied to large and/or hairy areas; powders may be used on feet, groin and other intertriginous areas (also inside socks and shoes)
- family members should be evaluated for asymptomatic carriage, particularly if infection is persistent or recurrent

Cutaneous candidiasis
Usually caused by the yeast, C. albicans, although other Candida species are occasionally responsible. Infections commonly occur in the groin, axillae, beneath the breasts, in abdominal folds in obese people, or in the umbilicus. Infections involving the nail are discussed in Nail infections.

Before starting treatment
Confirm diagnosis by microscopy and culture when systemic treatment is anticipated.
Manage predisposing factors such as diabetes, obesity, use of systemic corticosteroids or antibacterials, neutropenia, HIV, other immunocompromised states, occlusion, warm or moist environments, mechanical irritation and skin diseases, eg psoriasis.

Drug choice
Topical treatment
Immunocompetent patients can usually be treated with topical antifungal agents, including the azoles, nystatin and terbinafine.
Azoles (eg clotrimazole, miconazole) are the treatment of choice; are relatively broad spectrum, primarily fungistatic, generally considered more effective than topical nystatin and well tolerated; available as cream, lotion, solution, spray and powder.
Nystatin is available as a cream or ointment; not active against dermatophytes.
Terbinafine is fungistatic against Candida spp.; alternative to topical azoles, but more expensive; available as gel and cream.

Systemic treatment
Systemic treatment with azole antifungals is indicated for widespread or unresponsive disease and immunocompromised patients.
Fluconazole is the treatment of choice.
Itraconazole has similar safety profile to fluconazole; its use in candidal infections is less well studied.
Ketoconazole is highly effective, but due to its serious adverse effects, other oral azoles are preferred.

Other drug treatment
Topical corticosteroids may be used sparingly for short periods with topical and/or systemic antifungals, to reduce inflammation.

Practice points
- give advice about good hygiene, keeping the skin as clean and dry as possible (particularly the groin, armpits and skin folds) and avoiding occlusion
- creams are generally preferred; lotions or sprays may be applied to large and/or hairy areas; powders may be used on feet, groin and other intertriginous areas as well as inside socks and shoes
- continue treatment with topical azoles or nystatin for 2 weeks after symptoms resolve
- regular application of topical drugs is essential for successful treatment

13.03.01 Imidazoles (Skin)

Clotrimazole (Skin)
Mode of action
Impair biosynthesis of ergosterol for cytoplasmic membrane, inhibiting fungal growth; fungistatic.

Indications
Dermatophytoes
Mucocutaneous candidiasis, including paronychia
Pityriasis versicolor

Specific considerations
Pregnancy: Safe to use; ADEC category A.
Lactation: Safe to use.

Adverse effects
Topical imidazoles are generally well tolerated.
Infrequent: burning, stinging, itch, erythema
Rare: allergic reactions

Dosage
Apply sparingly twice a day.

Patient counselling
Regular application is essential for successful treatment.
Complete the full treatment course even if signs of infection have gone.
Attention to hygiene is important in the management of fungal disease of the feet; after washing, dry feet thoroughly, especially between toes.

Practice points
- continue treatment for 2–4 weeks in dermatophytoses
- use sparingly, especially in intertriginous areas, to avoid maceration
- creams are preferred; powders may be used on feet, moist lesions of the groin and intertriginous areas with creams or to prevent reinfection
- intractable candidiasis may be the presenting symptom of undiagnosed diabetes; appropriate urine and blood tests may be indicated in patients not responding to treatment
- topical imidazoles are not usually successful in treating infections of the nails or hair

Products
CLOTRIMAZOLE CREAM 20-30 GM TUBE (CLOTREX®, CLOTRIM®)

HYDROCORTISONE (SKIN)
Mode of action
Anti-inflammatory, immunosuppressive and antimitotic activity against cutaneous fibroblasts and epidermal cells. They are also vasoconstrictive.

Indications
Inflammatory skin conditions
Combination with clotrimazole or miconazole
Inflamed fungal skin infections
Relief of inflammation and itch in conditions such as eczema and psoriasis

Contraindications
Rosacea
Acne vulgaris
Allergy to product ingredients
Ulcerative skin conditions or impaired circulation
Uncontrolled infection in area to be treated

Specific considerations
Skin atrophy: increases systemic absorption and skin atrophy worsens; avoid use.
Diabetes: systemic absorption increases blood glucose concentration; avoid extensive use.
Impaired T cell function: systemic absorption results in immunosuppression; avoid extensive use.
Elderly: Skin atrophy makes cutaneous adverse effects more likely.
Children: Increased systemic absorption due to higher surface area/weight ratio. Skin permeability increased in neonates and infants.
Hydrocortisone is adequate initial treatment for most children with mild-to-moderate disease. Use more potent preparations for short periods under close supervision to regain control of disease.
Consider a corticosteroid-free period of at least 2 weeks after each 2–3-week period of daily use.
Pregnancy: Use the lowest appropriate potency of topical corticosteroid for the shortest time necessary where emollients and other simple measures are inadequate; betamethasone, hydrocortisone, methylprednisolone and triamcinolone ADEC category A; desonide and mometasone ADEC category B3 (safety data are lacking, use others in preference).
Breastfeeding: Safe to use; ensure breast area is free of corticosteroid before breastfeeding.

**Adverse effects**
Relative potency, patient age, site and extent of disease, preparation type, method of application and length of treatment determine the incidence and severity of adverse effects.
Common: folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, striae, purpura, depigmentation, telangiectasia
Infrequent: allergic contact dermatitis
Rare: hyperaesthesia, subcutaneous tissue atrophy, systemic effects (growth retardation, hypothalamic-pituitary-adrenal axis suppression, hyperglycaemia, Cushing's syndrome, cataract)

**Dosage**
Apply a thin layer 1–2 times a day.

**Patient counselling**
Apply a thin layer by smoothing gently into skin, preferably after bathing.

**Practice points**
- used in a range of skin conditions including insect bite reactions and sunburn

**Products**

HYDROCORTISONE ACETATE CREAM 1 % + MICONAZOLE 2 % CREAM 15 GM TUBE
(CANDICORT®, MICOVER -H®, MYCOHEAL -HC®)

ISOCONAZOLE (SKIN)

**Antimicrobial Action**
Isoconazole is an imidazole antifungal active against a wide spectrum of fungi including Candida spp., dermatophytes, and Malassezia furfur. It is also active against some Gram-positive bacteria.

**Uses and Administration**
Isoconazole nitrate is an imidazole antifungal used locally in the treatment of vaginal mycoses, particularly due to Candida spp. and in fungal skin infections. For vaginal infections it is usually given as pessaries in a single dose of 600 mg or 300 mg daily for 3 days, or as a 1% vaginal cream daily for 7 days. For skin infections a 2% cream or other topical formulation has been used

**Adverse Effects and Precautions**
Local reactions including burning or itching may occur following the application of isoconazole.
Intravaginal preparations of azole antifungals may damage latex contraceptives and additional contraceptive measures are therefore necessary during local administration of isoconazole.

**Precautions**
See Fluconazole.

**Products**

ISOCONAZOLE CREAM 1 % (AS NITRATE) 20 GM TUBE (AZONIT®, TRAVOGEN®)

KETOCONAZOLE (SKIN)

**Mode of action**
Impair biosynthesis of ergosterol for cytoplasmic membrane, inhibiting fungal growth; fungistatic.

**Indications**
Dermatophytoses
Mucocutaneous candidiasis, including paronychia
Pityriasis versicolor
Seborrhoeic dermatitis, see Seborrhoeic dermatitis in adults

**Specific considerations**
Pregnancy: Avoid use; use alternative imidazole; ADEC category B3.
Lactation: Safe to use.

**Adverse effects**
Topical imidazoles are generally well tolerated.
Infrequent: burning, stinging, itch, erythema
Rare: allergic reactions

**Dosage**
Dermatophytoses and cutaneous candidiasis
Apply sparingly twice a day.
Seborrhoeic dermatitis
Use shampoo twice a week for 4 weeks.

**Patient counselling**

Regular application is essential for successful treatment.

Complete the full treatment course even if signs of infection have gone.

Attention to hygiene is important in the management of fungal disease of the feet; after washing, dry feet thoroughly, especially between toes.

**Practice points**

- continue treatment for 2–4 weeks in dermatophytoses
- use sparingly, especially in intertriginous areas, to avoid maceration
- creams are preferred; powders may be used on feet, moist lesions of the groin and intertriginous areas with creams or to prevent reinfection
- intractable candidiasis may be the presenting symptom of undiagnosed diabetes; appropriate urine and blood tests may be indicated in patients not responding to treatment
- topical imidazoles are not usually successful in treating infections of the nails or hair

**Products**

KETOCONAZOLE SHAMPOO 0.02 % 100 ML BOTTLE (FUNGIPAN®, KETODAR®, NIZORAL®, PHILAZOLE®)

**MICONAZOLE (SKIN)**

**Mode of action**

Impair biosynthesis of ergosterol for cytoplasmic membrane, inhibiting fungal growth; fungistatic.

**Indications**

Dermatophytoses
Mucocutaneous candidiasis, including paronychia
Pityriasis versicolor
Seborrhoeic dermatitis (shampoo)

**Specific considerations**

Pregnancy: Safe to use; ADEC category A.
Lactation: Safe to use.

**Adverse effects**

Topical imidazoles are generally well tolerated.

Infrequent: burning, stinging, itch, erythema
Rare: allergic reactions

**Dosage**

Apply sparingly twice a day.

**Patient counselling**

Regular application is essential for successful treatment.

Complete the full treatment course even if signs of infection have gone.

Attention to hygiene is important in the management of fungal disease of the feet; after washing, dry feet thoroughly, especially between toes.

**Practice points**

- continue treatment for 2–4 weeks in dermatophytoses
- use sparingly, especially in intertriginous areas, to avoid maceration
- creams are preferred; powders may be used on feet, moist lesions of the groin and intertriginous areas with creams or to prevent reinfection
- intractable candidiasis may be the presenting symptom of undiagnosed diabetes; appropriate urine and blood tests may be indicated in patients not responding to treatment
- topical imidazoles are not usually successful in treating infections of the nails or hair
13.04 SCABICIDES AND PEDICULICIDES

SCABIES
Rationale for drug use
Scabies eradication.

Symptom relief.
Prevent secondary infection.
Prevent transmission.

Before starting treatment
Confirm diagnosis by demonstrating the typical burrows; or definitively, the mite, an ovum or scybalum (faecal pellet) by microscopy. Dermatoscopy may also be useful.

Drug choice
Permethrin 5%: treatment of choice (including in pregnancy and breastfeeding); pyrethroid insecticide; low toxicity and high efficacy; may cause irritation or allergic reaction.
Benzyl benzoate: messy; irritant; dilution required if used in children.
Crotamiton: other more effective agents preferred; may be used to control itch after treatment with a more effective scabicide; may cause irritation.
Maldison: alcohol-based lotion may cause irritation.

Special cases
Norwegian scabies is a severe crusted form that occurs rarely; immunocompromised or incapacitated patients are more susceptible; multiple applications are needed and combination treatment with keratolytics may be required. Resistant cases or immunocompromised, oral ivermectin may be beneficial.

Patient counselling
The affected person, all household/family members and close contacts should be treated at the same time to avoid becoming infected again. Even contacts who don't have any symptoms need to be treated.
Treatment with permethrin requires 2 applications 1 week apart.
Soft toys, bed linen and clothing should be washed and dried on hot machine settings the morning after each treatment or stored in tightly sealed plastic bags for 1–2 weeks.

Practice points
- examine patients 2 weeks after start of treatment to monitor adequacy; assess for irritant dermatitis and treat residual itch
- evidence of a cure requires follow-up for about 1 month; this is the time it takes for lesions to heal and for any eggs and mites to reach maturity if treatment fails
- improvement usually occurs within 1 or 2 days of treatment; itch generally lasts 2–3 weeks and patients should be warned not to mistake this for ongoing infection; manage the itch with moisturiser, topical corticosteroids, crotamiton or an antihistamine; patients should see a doctor if itching continues longer than 2–3 weeks

HEAD LICE
Pediculosis or infestation by the head louse, Pediculus humanus capitis, can occur at any age but is most common in school-age children.

Before starting treatment
A living, moving louse must be found to confirm infestation. Itching or the presence of eggs (nits) does not necessarily indicate active infestation.
Examine family members and close contacts for infestation. Family members with head lice should be treated at the same time.

Drug choice
If using chemical treatment use only products containing the insecticides mentioned below. Chemical resistance is common; check lice are killed the day after the first treatment and repeat successful treatment; if lice are not killed use a different insecticide as soon as possible.
Permethrin 1%: safe and effective; short application time (10 minutes); treatment of choice in pregnancy and breastfeeding.
Maldison: organophosphate pesticide; safe and effective when used as directed; avoid use in pregnancy and infants
Pyrethrins with piperonyl butoxide: probably as effective as other insecticide treatments.

Other treatment

'Bug busting': meticulous wet combing (using a special fine-tooth comb) with conditioner, can be used to detect and treat head lice. Although it provides an alternative to insecticide treatment evidence for benefit is unreliable and it requires motivation to be effective. Repeat every 2 days until there are no head lice seen for 10 consecutive days.

Electrified comb: despite a lack of clinical evidence there is anecdotal evidence that regular use of an electrified comb (available at most pharmacies) may be a useful non-drug alternative. This technique has the advantage of being less time consuming, does not damage hair and avoids the smell and cosmetic problems associated with topical preparations.

Essential oils, herbal products: there is insufficient evidence to support their use in eradicating lice.

Treatment failure

May result from inadequate or incorrect application, reinfection or pediculicide resistance.

Patient counselling

Check other family members for head lice. Only treat if a live louse is found.

Chemical treatment requires 2 applications 7 days apart. The second treatment kills the lice that have hatched since the first application.

Wet combing (using a special fine-tooth comb and conditioner) every 2 days in between chemical treatments may increase effectiveness, but avoid using conditioner for at least 1 day before and after chemical treatment. Wet combing, unlike chemical treatment, also helps to remove nits.

Do not use a hair dryer following chemical treatment as heat can destroy the active ingredient.

Children can be sent back to school after the first treatment. Tell children not to share hats and hairbrushes. Long hair should be tied back or plaited, especially while at school.

Soak combs and hairbrushes in hot water (＞60°C) for 30 seconds and wash pillowcases in hot water or put in a clothes dryer for 15 minutes.

Do not overuse chemical treatments or use them to prevent head lice infestation. Overuse can cause irritation and result in lice that are resistant to chemical treatment.

BENZYL BENZOATE

Mode of action

Unknown.

Indications

Scabies, Pediculosis

Contraindications

Acutely inflamed skin, or raw, weeping skin

Allergy to benzyl benzoate

Specific considerations

Elderly: Age-related dryness of skin increases susceptibility to drying effects of benzyl benzoate; irritation may be worse in this age group.

Children: Dilute with an equal quantity of water for children <12 years and with 3 parts of water for infants. Dilution reduces irritation, but also efficacy.

Pregnancy: Although no problems in humans have been documented with benzyl benzoate, use of permethrin is preferred; ADEC category B2.

Lactation: Data lacking, permethrin preferred.

Adverse effects

Infrequent: burning sensation, itch and dermatitis

Rare: CNS stimulation, eg convulsions (with excessive topical use), allergic reaction

Dosage and administration instructions

Test on small area of skin for 10 minutes before using. If excessive stinging occurs, it should be diluted with an equal quantity of water, then retested before using.

Scabies

Apply to cool skin (not hot after bathing) from chin down; repeat without bathing on the following day and wash off 24 hours later; a third application may be required in some cases.

In infants and young children up to 2 years, also apply to the scalp, neck, face and ears; avoid eyes, mouth and mucous membranes.

Pediculosis: Coat affected region and leave on for 24 hours, then wash with soap and water.
**Patient counselling**
Do not use on face unless advised by your doctor; avoid contact with eyes, mouth and mucous membranes. If you wash your hands or any other part of your body during the treatment period for scabies, you should reapply the lotion to the washed areas. Itch may persist for some months after scabies treatment (7–10 days after lice treatment); this may not be ongoing infection although persisting itch could mean scabies that has not responded. Symptomatic itch treatment may be required.

**Practice points**

**Scabies**
- benzyl benzoate has been superseded by more effective products for the treatment of scabies (50% cure rate with benzyl benzoate versus 80% with permethrin)
- improvement usually occurs within 1 or 2 days of treatment
- traditionally applied after a bath, but this is unnecessary and may increase transdermal absorption, removing drug from site of action and increasing the risk of systemic toxicity
- special attention should be given to the finger and toe webs, under nails, umbilicus, intertriginous areas and intergluteal cleft
- application to the genitals is irritant; use another insecticide (eg permethrin) or relieve with hydrocortisone 1% cream
- scalp, neck, face and ears may also need to be treated in elderly, immunocompromised, people who have had treatment failure or those with atypical or crusted scabies; stinging is significant; an alternative agent may be preferable
- do not use to prevent scabies

**Pediculosis**
- efficacy is questionable; other agents are more effective

**Products**

**BENZYL BENZOATE LOTION 25% 100 ML BOTTLE (BENZYL BENZOATE®)**

**CROTAMITON**

**Mode of action**
Unknown.

**Indications**
Scabies (but not pediculosis)
Itch from various causes, eg post-scabies and post-pediculosis itch, insect bites (claims of drug's antipruritic activity based largely on uncontrolled studies)

**Contraindications**
Acutely inflamed skin or raw, weeping skin
Allergy to crotamiton

**Specific considerations**
- Pregnancy: Safe to use; ADEC category B2.
- Lactation: Safe to use (avoid nipple region).

**Adverse effects**
- Infrequent: irritation
- Rare: allergic reaction

**Dosage**
Scabies, apply once a day for 2–5 days, preferably in the evening; do not wash off until next application is due.
Itch, apply 2–3 times a day.

**Administration instructions**
Scabies, after bathing and drying, allow skin to cool before applying to body from chin down.
Special attention should be given to the finger and toe webs, under nails, umbilicus, intertriginous areas and intergluteal cleft.
Itch, rub into affected areas.

**Patient counselling**
Do not use on face; avoid contact with eyes, mouth and mucous membranes.
Massage into skin until dry, do not wash off for 24 hours.
If you wash your hands or any other part of your body during the treatment period for scabies, you should reapply the lotion/cream to the washed areas.
Do not apply to entire body surface of small children more than once daily.

**Practice points**
- other more effective agents, eg permethrin, are usually preferred in the treatment of scabies
- if used correctly, 2 applications of crotamiton may be effective in eradicating scabies

**Products**
- CROTAMITON CREAM 10% 20-25 GM TUBE (CROTAPHIL®, EURAX®)
- CROTAMITON LOTION 10% 50 ML BOTTLE (CROTAPHIL®, EURAX®)

**PYRETHRIN**

**Mode of action**
Pyrethrins are absorbed through the chitinous exoskeleton of arthropods and stimulate the nervous system. Nerve impulse transmission is blocked, resulting in paralysis and death.
Piperonyl butoxide inhibits pyrethrin metabolism in arthropods (it has little or no insecticidal activity).

**Indications**
- Pediculosis

**Contraindications**
- Allergy to pyrethrins or pyrethroids
- Acute inflamed skin

**Specific considerations**
- Pregnancy: Permethrin preferred; ADEC category B3.
- Lactation: Safe to use.

**Adverse effects**
Rare: allergic reaction, skin infection, skin irritation

**Dosage**
Following initial treatment, a second treatment is required in 7–10 days to kill any newly hatched lice.

**Administration instructions**
- Mousse: Apply to dry hair and massage in until wet; leave for 10 minutes, then wash out with shampoo.
- Aerosol spray: Moisten whole scalp by spraying in short bursts (2–3 seconds); leave for 30 minutes (do not cover head), then wash out with shampoo.

**Patient counselling**
- Apply aerosol in a well ventilated room.
- Avoid contact with eyes, mouth and mucous membranes.
- Avoid excessive treatment, as irritation can occur.
- Do not use on eyelashes or eyebrows; check with your doctor or pharmacist if they become infested.
- Wash hands immediately after using medication.

**Practice points**
- treatment should be repeated in 7–10 days to kill any newly hatched lice

**Products**
- PYRETHRINE SHAMPOO 0.165% 100 ML BOTTLE (LICESOL®)

**13.05 DRUGS FOR OTHER SKIN INFECTIONS**

**13.05.01 Antibacterials (Skin)**

**FUSIDIC ACID (SODIUM FUSIDATE) (SKIN)**

**Indications**
- Staphylococcal skin infections

**Specific considerations**
- Pregnancy: Avoid use during the last month of pregnancy; ADEC category C.

**Adverse effects**
Rare: hypersensitivity reactions including rash and irritation

**Dosage**
Apply 2–3 times daily for 7 days. If using a protective dressing, apply once daily.

**Patient counselling**
- Avoid contact with eyes.
- Exclude child with impetigo from school until appropriate treatment is started. Sores on exposed surfaces must be
covered with a watertight dressing.

**Practice points**
- Avoid use in chronic skin conditions because of doubtful efficacy and risk of resistance emerging during treatment
- Studies comparing topical sodium fusidate and mupirocin show no significant difference in efficacy in staphylococcal skin infections; mupirocin is preferred for mild impetigo

**Products**
- **Fusidic Acid Cream 2%** 15 GM TUBE (DERMOFUCIN®, FUCIDIN®, FUSIDERM®, FUSIVER®, TOPIDIC®, UCIDERM®)
- **Fusidic Acid Cream 2% + Betamethasone (as valerate) Cream 0.1%** 15 GM TUBE (FUCICORT®)
- **Fusidic Acid Gel 2%** 15 GM TUBE (DERMOFUCIN®, FUCIDIN®, TOPIDIC®, UCIDERM®)
- **Fusidic Acid Ointment 2%** 15 GM TUBE (DERMOFUCIN®, FUCIDIN®, FUSIDERM®, FUSIVER®, TOPIDIC®, UCIDERM®, ZETA®)

**Metronidazole (Skin)**

**Indications**
Acne rosacea

**Specific considerations**
- Pregnancy: Safe to use; ADEC category B2.
- Lactation: Safe to use.

**Adverse effects**
Common: local reactions include eye irritation (watering), redness, dryness and skin irritation

**Dosage**
Rub a thin film of gel or cream into affected areas twice a day.

**Administration instructions**
Apply to clean, dry skin. Avoid eye area.

**Practice points**
- Use with systemic treatment or alone for mild rosacea and maintenance therapy
- There should be improvement within 3 weeks; continue treatment for 8–9 weeks
- Continued topical therapy after oral tetracycline is stopped lowers the relapse rate

**Products**
- **Metronidazole Gel 0.75%** 15-25 GM TUBE (FLANIZOL®, METROZA®)

**13.05.02 Antivirals (Skin)**

**Aciclovir (Skin)**

**Indications**
Labial herpes simplex (cold sores), initial and recurrent

**Specific considerations**
- Immunocompromised patients: oral aciclovir is more effective than topical.
- Pregnancy: Safe to use; ADEC category B3.
- Lactation: Safe to use.

**Adverse effects**
Common: dry or flaking skin, transient stinging or burning
Infrequent: erythema, itch
Rare: allergic dermatitis

**Dosage**
Apply at first sign of lesion; apply 5 times a day (every 4 hours while awake) for 5 days.

**Administration instructions**
Avoid contact with eyes and mucous membranes.

**Practice points**
- Treat as early as possible in the course of infection
- Treatment of primary infections relieves symptoms and reduces duration of viral shedding, but does not affect recurrence rate
- More effective for primary infections than for recurrences
Products
ACICLOVIR CREAM 5% 2 GM TUBE (CYCLOHERP®, CUSIVIRAL®, HERPAVIR®, ZOVIRAX®, SUPRAVIRAN®)

13.06 DRUGS FOR PSORIASIS

PSORIASIS
Psoriasis is a common inflammatory and proliferative disease. Several morphological variants exist; plaque psoriasis is the most common and classically affects elbows, knees, buttocks and scalp.

Rationale for drug use
Induce remission.
Reduce the severity and extent of psoriasis to a tolerable level.
Relieve symptoms, including itch, excessive scale, pain.

Before starting treatment
Minimise or eliminate potential trigger factors where possible, eg stress, trauma, smoking, alcohol, infection (streptococcal throat infection may precipitate guttate psoriasis). Drugs known to exacerbate or trigger psoriasis include lithium, quinolines, ACE inhibitors, NSAIDs and beta-blockers.
Consider referral to a dermatologist if the diagnosis is in doubt, therapy fails, or when treatment with phototherapy or systemic agents is indicated.

When to start treatment
Troubling local symptoms, eg pain, itch, reduced manual dexterity, flexural intertrigo.
Cosmetic problems, eg prominent hand, arm, leg or facial lesions.

Drug choice
Topical treatment
Should be the initial treatment for stable plaque psoriasis, except when large areas of involvement make this impractical or expensive. Topical agents are commonly used in combination. A patient who does not respond to a particular agent may respond to it in the future.

Moisturisers
Moisturisers hydrate and soften the scaly, hyperkeratotic surface of psoriatic plaques and may suffice in mild disease or in some patients with more extensive disease who prefer a treatment with minimal adverse effects.

Keratolytics
Include salicylic acid. They help to remove accumulated scale and allow other topical agents such as coal tar, dithranol and corticosteroids to penetrate lesions. They can cause irritation.

Coal tar
Coal tar is generally preferred for limited or scalp psoriasis but can be effective in widespread psoriasis, eg guttate psoriasis. May not clear psoriasis as quickly as other topical agents but remission may be longer. Crude tar preparations are difficult to apply, stain clothing and smell unpleasant; newer, more refined preparations are less messy but may be less effective. It is photosensitising and may be irritant to face, genitals, flexures and in unstable psoriasis.

Dithranol
Dithranol may be used in increasing strength and contact duration according to patient response and tolerance. Treatment is more feasible when plaques are large or few. Short contact treatment with higher dithranol concentrations is as effective as overnight application of lower concentrations. It is irritant and stains clothing, skin and hair.

Topical corticosteroids
Topical corticosteroids have quicker onset of action than coal tar and dithranol. May be useful when treating face, flexures and genitals (where coal tar and dithranol are contraindicated), in localised disease and in scalp psoriasis. Tachyphylaxis develops with continued use and relapse occurs faster than with other topical treatments. There is a risk of local and systemic adverse effects; should not be used in extensive disease or in large amounts for periods >4–6 weeks (trunk), >4 weeks (palms or soles) or >few days to 1 week (face or flexures). Potent topical corticosteroids should be used with caution. Systemic corticosteroids are not prescribed due to the risk of rebound flare.

Calcipotriol
Calcipotriol is useful in the treatment of resistant plaque psoriasis; similar efficacy to moderate potency.
corticosteroids and coal tar; tolerance does not occur; continuous use beyond 12 months has not been studied. Can cause irritation particularly if applied to face or skin folds.

**Phototherapy**

**UVB light**

Narrow band UVB is the preferred form of phototherapy for psoriasis. Safer, simpler and cheaper than photchemotherapy. UVB may be used alone or with topical treatments, eg coal tar, dithranol or calcipotriol. Particularly effective in guttate psoriasis when used alone.

**Photochemotherapy (PUVA)**

Combines topical or oral methoxsalen with UVA; probably the least toxic of all systemic agents. Its advantages are a high likelihood of response and no need for topical medication between treatments. There is a potential risk of non-melanoma skin cancer with PUVA. It is reserved for severe psoriasis unresponsive to other treatments.

**Systemic treatment**

Acitretin and immunomodulators have potentially serious adverse effects and drug interactions; they should not be used in pregnancy and their use should be overseen by a dermatologist.

**Acitretin**

Acitretin is most effective in treating pustular and erythrodermic psoriasis; less effective in treating plaque psoriasis. 10–20% discontinuation rate due to adverse effects and risk of teratogenicity make acitretin less acceptable to women who may become pregnant. May be combined with phototherapy or calcipotriol, providing increased efficacy and an acitretin-sparing effect.

**Immunomodulators**

Methotrexate and cyclosporin are used most frequently; they are indicated in extensive plaque psoriasis and psoriasis refractory to topical treatment, generalised pustular or erythrodermic psoriasis and severe psoriatic arthritis. Mycophenolate mofetil and tacrolimus are newer agents that may be useful in selected patients, seek specialist advice.

Hydroxyurea is used occasionally but is less effective than methotrexate or cyclosporin.

Alefacept and efalizumab have recently been approved for the treatment of moderate-to-severe psoriasis. They have not been directly compared with other systemic agents and long term safety and efficacy have not been established. Reserve for patients with contraindications to, or who are unresponsive to, phototherapy or systemic therapy.

**Other treatments**

**Antimicrobials**

Indications include secondary skin infections and psoriasis precipitated by infection.

**Combination therapy**

Useful when monotherapy has failed, to limit toxicities of individual agents (lower dosages can be used) and to improve therapeutic outcome (combination more effective than either agent alone). Usually one agent is stopped after psoriasis has cleared and the safer agent is continued as maintenance treatment.

Examples of combinations include coal tar or dithranol with UVB, acitretin with UVB or PUVA, methotrexate with UVB or cyclosporin.

**Rotational therapy**

Rotating treatment regimens, before significant individual drug toxicities occur, minimizes chronic toxicity and facilitates long term treatment.

Primary agents include PUVA, methotrexate, acitretin, UVB (with or without coal tar or dithranol) and cyclosporin. Secondary agents such as hydroxyurea may be tried when the primary agents are no longer effective or have unacceptable side effects.

**Special cases**

Unstable psoriasis: Trigger factors include intensive systemic and topical corticosteroids, infection and overtreatment with tar, dithranol or ultraviolet irradiation. It often warrants hospitalisation for systemic treatment with retinoids or immunosuppressants and skilled nursing.

Scalp psoriasis: Coal tar and dithranol preparations with or without salicylic acid and/or sulfur, calcipotriol or corticosteroid scalp lotions may be used.

**CALCIPOTRIOL**

**Vitamin D analogue**

Also known as calcipotriene.

**Mode of action**

Vitamin D analogue. Induces differentiation and suppresses proliferation of keratinocytes, reversing the abnormal keratinocyte changes in psoriasis.

**Indications**
Psoriasis vulgaris, chronic stable plaque type

Contraindications
Disorders of calcium metabolism
Previous allergic reaction to calcipotriol
Severe, extensive psoriasis (in view of the risk of hypercalcaemia secondary to excessive absorption)
Specific considerations
Renal impairment: Data lacking, unlikely to be of concern; monitor plasma concentrations.
Hepatic impairment: Safety not established.
Pregnancy: Data lacking; contact specialised information service.
Lactation: Ensure chest area is free from calcipotriol for breastfeeding, to avoid possible transfer to infant.

Adverse effects
Common: skin irritation (usually mild burning or stinging)
Infrequent: erythema and scaling
Rare: allergic contact dermatitis, hypercalcaemia, photosensitivity, changes in pigmentation

Dosage
Apply to affected area twice a day. Less frequent application may be adequate after initial period. Stop treatment after satisfactory improvement; reinstate if disease recurs.
Maximum
Adult
Cream or ointment, 5 mg calcipotriol (100 g) each week.
Liquid, 3 mg calcipotriol (60 mL) each week. >1 formulation, 5 mg calcipotriol each week.
Child
6–12 years, ointment, 50 g each week for up to 8 weeks.
>12 years, ointment, 75 g each week for up to 8 weeks.
Combination with betamethasone
For additional information see BETAMETHASONE (skin)
Adult, apply to the affected area once daily. Maximum of 100 g each week. Do not apply to >30% of body surface.

Patient counselling
Do not mix with other preparations unless instructed; mixing can destroy the calcipotriol.
Wash hands thoroughly after applying to avoid unintentional transfer to other body areas.
Do not apply to face; itch and redness occurs.
Protect treated areas from sunlight with protective clothing or sunscreen. Broad spectrum sunscreen, at least factor 15+, containing a physical agent (eg titanium dioxide) is recommended. Avoid sunlamps and tanning beds.

Practice points
- calcipotriol is unstable in the presence of salicylic acid or UVA; to avoid loss of efficacy:
  - apply salicylic acid at a different time of day
  - apply calcipotriol after UVA treatment
- may need to use calcipotriol for 4–6 weeks for maximum improvement
- avoid use on skin folds, face and scalp, which are especially susceptible to irritation
- avoid use with calcium or vitamin D supplements or drugs that increase the systemic availability of calcium (eg calcium-containing antacids, thiazide diuretics)
- monitor plasma calcium and renal function every 3 months; if calcium is elevated, stop treatment and monitor calcium level each week until normal; may continue treatment with regular monitoring if the elevation is marginal
- plasma calcium monitoring may not be required if patients are applying <30 g each week
- to minimise risk of hypercalcaemia, use <100 g each week
- calcipotriol may be used with UVB, PUVA, retinoids and immunosuppressants, allowing less frequent and lower dosing of these agents, thus minimising their adverse effects
- there are limited data on the use of calcipotriol with betamethasone beyond a month; change to a single ingredient product after 4 weeks of treatment

Products
CALCIPOTRIOL CREAM 50 MCG 30 GM TUBE (DAIVOBET®)
CALCIPOTRIOL OINTMENT 50 MCG 30 GM TUBE (DAIVOBET®)
CALCIPOTRIOL OINTMENT 50 MCG + BETAMETHASONE 30 GM TUBE (DAIVOBET®)
CALCIPOTRIOL SCALP SOLUTION 50 MCG/ML 30 ML BOTTLE (DAIVONEX®)
HYDROQUINONE

Adverse Effects, Treatment, and Precautions
Topical hydroquinone may cause transient erythema and a mild burning sensation. High concentrations or prolonged use may produce hyperpigmentation especially on areas of skin exposed to sunlight. Occasionally hypersensitivity has occurred and some recommend skin testing before use. Hydroquinone should not be applied to abraded or sunburnt skin. It should not be used to bleach eyelashes or eyebrows and contact with the eyes should be avoided as it may produce staining and corneal opacities. The systemic effects of hydroquinone and their treatment are similar to those of phenol but tremors and convulsions may also occur.

Uses and Administration
Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. Hydroquinone is used topically as a depigmenting agent for the skin in hyperpigmentation conditions such as chloasma (melasma), freckles, and lentigines (small macules that resemble freckles). Concentrations of 2 to 4% are commonly used; higher concentrations may be very irritant and increase the risk of ochronosis. It may be several weeks before any effect is apparent but depigmentation may last for 2 to 6 months after discontinuation. Application of hydroquinone should be discontinued if there is no improvement after 2 months. Hydroquinone should be applied twice daily only to intact skin which should be protected from sunlight to reduce repigmentation. Hydroquinone preparations often include a sunscreen or a sunblocking basis.

Hydroquinone is also used as an antioxidant for ether and in photographic developers.

Products
HYDROQUINONE CREAM 4% 30 GM TUBE (ECLADERM®, ELDOQUIN®, FEDIQUIN®, PHILAQUIN®)

METHOXSALEN
Psoralens
Mode of action
The therapeutic effect of UVA-activated psoralens for psoriasis probably involves binding to DNA and inhibition of DNA synthesis, resulting in decreased cell proliferation. In the absence of UV light, psoralens are inert.

Indications
Photosensitizers before UVA phototherapy in the following conditions:
Marketed: Vitiligo
Accepted: Psoriasis, severe, refractory, disabling
Atopic eczema: Polymorphic light eruption
T cell lymphomas, eg mycosis fungoides

Contraindications
Conditions associated with photosensitivity, eg porphyria, xeroderma pigmentosum, lupus erythematosus
Aphakia (increased risk of retinal damage due to lack of lenses)
Cataracts
Melanoma, invasive squamous cell carcinoma

Specific considerations
Treatment with photosensitising medications: increases risk of phototoxic and photoallergic reactions; avoid combination.
Hepatic impairment: Use cautiously.
Children: Should not be used in children; safety not established.
Pregnancy: Avoid use; ADEC category B2.
Lactation: Avoid use; safety not established.

Adverse effects
Common: Oral psoralens, itch, nausea, erythema
Infrequent: Oral, CNS effects (including nervousness, insomnia, depression)
Topical, contact allergy
PUVA therapy
itch, mild transient erythema, oedema, vesication, bullae formation, onycholysis, acneiform eruptions,
hypertrichosis, pigmentation alterations, exacerbation of systemic lupus erythematosus
Long term effects, premature skin ageing, cutaneous carcinogenesis, cataract formation
Severe burns may result from overexposure to sunlight or UVA radiation.

Dosage
Oral, 0.6 mg/kg taken with milk or after food, 2 hours before UV light exposure.
Lotion, apply a 1:10 dilution of the 1% lotion (resulting in a 0.1% preparation) to affected areas 30 minutes before UV light exposure.

**Patient counselling**

Do not sunbathe for 24 hours before and 48 hours after, PUVA therapy.

Most people have 20–30 PUVA treatments.

After taking methoxsalen, avoid exposure to sunlight, even through glass and cloud cover, for at least 8 hours. After application to the skin, exposure to sunlight should be avoided for at least 12–48 hours. If exposure to sunlight cannot be avoided, protective clothing should be worn and sunscreens applied to all areas that may be exposed, including lips.

Wear wrap-around sunglasses with 100% UVA-absorbing properties during daylight for 24 hours after taking methoxsalen, and after methoxsalen with UVA treatment, to avoid cataracts.

Certain foods contain natural photosensitisers, eg limes, figs, parsley, parsnips, mustard, carrots and celery; these must be eaten sparingly, or avoided, while taking methoxsalen.

**Practice points**

- PUVA treatments may be given 2 or 3 times a week, but must be at least 48 hours apart
- never dispense the lotion for home use
- if nausea occurs divide the oral dose in two and give 15 minutes apart
- cataracts may occur in patients who fail to wear suitable eye protection for 24 hours after oral treatment
- overexposure to sunlight or artificial UV emission after taking methoxsalen may result in serious burning
- ophthalmic examination, measurement of antinuclear antibody titre and hepatic function should be performed before and every 12 months after, beginning of treatment
- examine skin for malignancy every 6 months, depending on dose and duration of treatment
- topical treatment results in more prolonged photosensitivity, greater incidence of adverse effects and is less cosmetically acceptable than systemic treatment
- use of topical methoxsalen in psoriasis has largely been abandoned, except for psoriasis of the hands and feet or localised chronic plaques

**Products**

METHOXSALEN CAPS 10 MG (OXSORALEN®)

### 13.07 DRUGS FOR WARTS AND CALLUSES

**WARTS**

Warts are caused by human papilloma virus (HPV). Different HPV genotypes infect particular locations and only some are associated with neoplasia. Warts are commonly classified according to location and morphology.

Cutaneous warts include common, flat, mosaic, plantar and palmar warts. Anogenital warts involve the vulva, vagina, cervix, penis, scrotum, urethra and rectum. Extracutaneous warts include oral and laryngeal lesions.

**Rationale for drug use**

Eradicate warts.

Stop spread to other sites or people.

Reduce unwanted local effects.

**Before starting treatment**

Discuss the need to remove cutaneous warts only when they are a cosmetic problem or causing unwanted effects as treatments are destructive and an immune response usually will remove the wart (30% disappear within 6 months and most disappear within 3 years without treatment in immunocompetent individuals).

Note current and past treatments, both successful and unsuccessful, and complications including pain, scarring, changes in pigmentation and extension of warts.

Consider possibility of adjacent mucous membrane involvement in patients with external anogenital warts; specialist referral for anoscopy or colposcopy may be indicated.

Consider factors that may predispose to HPV infection, eg immunosuppression.

Assess pregnancy status; podophyllotoxin and podophyllum resin are contraindicated in pregnancy and imiquimod should be avoided.

Encourage patients with anogenital warts to tell sexual partners and suggest they seek medical advice. Screening for other STIs may also be appropriate.

**When to start treatment**

Unwanted local effects, eg itch, burning, bleeding or painful coitus associated with genital warts; tenderness precluding weight bearing with plantar warts.
Cosmetic and psychosocial considerations.
Numerous and/or large warts.
Warts in immunocompromised patients, as may develop into squamous cell carcinomas.

**Drug choice**

There is no specific HPV antiviral and treatment relies on local tissue destruction or immune modification.

**Cutaneous warts**

Salicylic acid: treatment of choice; inexpensive and may be used at home; relatively safe with few complications. It is irritant and not suitable for application to the face or broken skin; reduce frequency of application if discomfort occurs. Use caution in diabetes and peripheral vascular disease.

Also available in combination with trichloracetic acid (Upton's paste) and lactic acid. The combination with lactic acid has not been shown to be more effective than salicylic acid alone.

Glutaraldehyde: reserve for plantar warts; irritant and not suitable for application to face or broken skin; stains skin brown; rarely used.

Podophyllum resin: available alone or in combination with salicylic acid; may cause severe systemic toxicity; use under close supervision.

**Anogenital warts**

Podophyllotoxin: treatment of choice; available as a paint for self-treatment of external genital warts; irritant but low systemic toxicity; compliance is important.

Imiquimod: modifies immune response; use for self-treatment of external genital warts; has the advantage of less frequent application and few adverse effects; clearance rates similar to established treatments.

**Other drug treatment**

Monochloroacetic acid, formaldehyde, nitric acid and silver nitrate are rarely used for cutaneous warts. Retinoids, intralesional bleomycin, interferon alfa or beta, contact immunotherapy, oral colchicine and cimetidine have been used in the treatment of cutaneous and anogenital warts but there is insufficient evidence of efficacy. There is some evidence of efficacy for topical fluorouracil but it is not superior to simpler treatments.

**Non-drug treatment**

Cryotherapy may be used for cutaneous and anogenital warts; multiple treatments required; painful (essentially preventing use in children); contraindicated in patients with cold intolerance; may cause scarring, dyspigmentation, infection and rarely, damage to underlying nerves.

Electrosurgery and curettage, blunt dissection, carbon dioxide laser are costly options for cutaneous and anogenital warts without distinct advantages; may be tried if topical agents or cryotherapy fail.

**Practice points**

- as some warts may regress spontaneously, no treatment may be an option
- HPV persists after treatment and a degree of infectivity may remain even in the absence of clinical lesions
- patients with cutaneous warts should be advised about ways to reduce the chance of spreading the infection (individual towels and avoiding skin maceration)
- plantar warts at pressure points should be treated with non-surgical methods to reduce risk of painful scarring
- in patients with diabetes, lesions may be best left untreated since poor circulation may result in infection
- specialist referral is required for oral, laryngeal, urethral, anorectal, vaginal and cervical (especially if cervical dysplasia present on Pap smear) warts

**Anogenital warts**

- patients with warts should use condoms particularly with new sexual partners as they protect against other STIs; however, condoms may only reduce the risk of HPV transmission
- HPV types that cause external visible warts are rarely associated with cervical abnormalities that can cause cancer; women should have regular cervical smears as part of the usual cervical screening program

**SALICYLIC ACID**

**Mode of action**
Keratolytic, weak antifungal and antibacterial actions.

**Indications**
Dandruff, Dermatitis, seborrhoeic, Ichthyosis, Psoriasis, Acne, Warts (cutaneous), corns and calluses, Fungal infections

**Contraindications**
Allergy to salicylic acid

Use on facial and anogenital warts, moles, birthmarks
Use on inflamed, broken or infected skin
Use in intertriginous areas

Specific considerations
Diabetes, peripheral vascular disease: acute inflammation or ulceration may occur, especially on feet.
Elderly: Age-related peripheral vascular disease makes acute inflammation and ulceration of the extremities more likely.
Children: At increased risk of toxicity because of increased absorption and increased ratio of treated area to total body surface area; lower threshold for skin irritation; do not use in neonates.
Pregnancy: Safe to use for warts; for other uses, contact specialised information service
Lactation: Safe to use for warts.

Adverse effects
Salicylate intoxication and death have resulted from the topical use of salicylic acid.
Factors that increase the risk of salicylate intoxication include age of patient, amount applied, frequency of application and occlusion (either naturally in skin folds or as occlusive dressings).
Infrequent: skin irritation
Rare: skin ulceration, erosion, salicylism (intoxication due to absorption; symptoms include confusion, dizziness, headaches, rapid breathing, tinnitus)

Dosage
Psoriasis, seborrhoeic dermatitis affecting body: Apply cream or lotion in a thin layer to affected areas 2–3 times a day.
Scalp psoriasis, dandruff, seborrhoeic dermatitis: Apply shampoo to wet hair and massage vigorously into scalp and leave for at least 3–5 minutes; rinse hair thoroughly after shampooing; repeat twice a week.
Warts, corns, calluses: Before application, clean affected area, soak wart in warm water for 5 minutes, remove loose tissue with a blade, pumice stone, cloth or emery board and dry thoroughly. Apply preparation to lesion only; contact with adjacent tissue may be reduced by encircling lesion with soft paraffin or a bandage.
Apply solution or cream 1–2 times a day.
Acne: Cleansing bar, lotion, lather with warm water and rinse off 2–3 times a day.
Wipes, wipe pad over affected area 2–3 times a day; do not rinse after treatment.

Patient counselling
Avoid contact with eyes, mouth and other mucous membranes.
Wash hands immediately after applying medication, unless hands are being treated.
Solutions for the removal of warts should not be used near heat or open flame or while smoking; avoid inhalation of vapours.

Practice points
- keratolytic activity of salicylic acid potentiates effects of topical corticosteroids, dithranol and tar by increasing their dermal penetration
- cumulative irritant or drying effect with abrasive or medicated soaps or cleansers, acne products, alcohol-containing preparations and medicated cosmetics; avoid combinations if possible
- to minimise systemic absorption following application, do not use for prolonged periods, in high concentrations, on large areas of the body, or on inflamed or broken skin
- to remove thick, adherent scales in psoriasis, creams or lotions may be used under occlusion overnight, eg using a plastic shower cap
- to avoid excessive drying, begin acne treatment with a single application daily and then, if necessary, increase frequency gradually; use cautiously with other topical acne preparations
- may be used with other agents such as coal tar (in eczema and psoriasis), dithranol (in psoriasis), lactic acid, trichloracetic acid and podophyllum resin (removal of warts)
- there is a lack of substantial evidence that the combination of lactic acid and salicylic acid is any more effective than salicylic acid alone in treating warts
Products
SALICYLIC ACID 20 % + LACTIC ACID 5 % + POLIDOCANOL 2 % TOPICAL LOTION 10 ML (COLLOMACK®)

13.08 MISCELLANEOUS

CALAMINE
Calamine has mild astringent and antipruritic actions and is used as a dusting powder, cream, lotion, or ointment in a variety of skin conditions although its value is uncertain.

Products
CALAMINE 15 %+ZINC OXIDE 5 % CREAM (VASOGEN®)
CALAMINE 15 %+ZINC OXIDE 5 % LOTION 200 ML BOTTLE (AL RAZI CALAMIN®)

EMOLLIENT CREAM AND OINTMENT

Products
EMOLLIENT CREAM
EMOLLIENT OINTMENT

SODIUM STIBOGLUCONATE

Pharmacokinetics
The pentavalent antimony compounds are poorly absorbed from the gastrointestinal tract. After intravenous doses an initial distribution phase is followed by biexponential elimination by the kidneys. The elimination half-life of the initial phase is about 1.7 hours and that of the slow terminal phase is about 33 hours. The corresponding half-lives after intramuscular doses are reported to be 2 hours and 766 hours respectively. Antimony has been detected in breast milk.

Uses and Administration
Pentavalent antimony, as sodium stibogluconate or meglumine antimonate, is used as first-line treatment for all forms of leishmaniasis except Leishmania aethiopica infections.

For systemic use, sodium stibogluconate is given by intramuscular or intravenous injection as a solution containing the equivalent of 100 mg of pentavalent antimony per mL. Intramuscular injection is generally preferable. Intravenous injections must be administered very slowly (over at least 5 minutes) and preferably through a fine needle to avoid thrombophlebitis; as with trivalent antimony compounds, they should be stopped immediately if coughing, vomiting, or substernal pain occurs. Meglumine antimonate is given by deep intramuscular injection as a solution containing the equivalent of 85 mg of pentavalent antimony per mL. Doses are expressed in terms of the equivalent amount of pentavalent antimony.

Local variations exist in treatment schedules but WHO recommends the following regimens:
In visceral leishmaniasis, initial treatment is based on daily injection of pentavalent antimony 20 mg/kg to a maximum of 850 mg for at least 20 days. The length of treatment varies from one endemic area to another, but is continued until no parasites are detected in consecutive splenic aspirates taken at 14-day intervals. Patients who relapse are re-treated at the same dose.

Early non-inflamed lesions of cutaneous leishmaniasis due to all forms of Leishmania except L. aethiopica, L. amazonensis, and L. braziliensis may be treated by infiltration with intralesionol injections of 1 to 3 mL of sodium stibogluconate or meglumine antimonate (approximately 100 to 300 mg of pentavalent antimony), repeated once or twice if necessary at intervals of 1 to 2 days. Systemic therapy with pentavalent antimony 10 to 20 mg/kg daily is given if the lesions are more severe and continued until a few days after clinical and parasitological cure is achieved. Cutaneous leishmaniasis due to L. aethiopica is not responsive to antimonials at conventional doses. In cutaneous leishmaniasis due to L. braziliensis, prolonged systemic treatment with pentavalent antimony 20 mg/kg daily for a minimum of 4 weeks is indicated. Similar doses are required for diffuse cutaneous leishmaniasis due to L. amazonensis and are continued for several months after clinical improvement occurs. Relapses should be expected until immunity develops.

In mucocutaneous leishmaniasis, daily doses of pentavalent antimony 20 mg/kg are given for a minimum of 4 weeks; if the response is poor, 10 to 15 mg/kg may be given every 12 hours. Relapses are well known and have generally been associated with inadequate or interrupted treatment; they are treated with the same drug given for at least twice as long as the original treatment. Only when that fails should alternative treatment be given.
Contraindications
Allergy to sodium stibogluconate
Significant impairment of renal function

Adverse Effects, Treatment, and Precautions
Adverse effects are generally less frequent and less severe with the pentavalent antimony compounds sodium stibogluconate and meglumine antimonate than with trivalent compounds such as antimony sodium tartrate. Nevertheless, similar precautions should be observed, especially in patients on high-dose therapy. Intramuscular injections of sodium stibogluconate can be painful and intravenous use has been associated with thrombophlebitis. Common side-effects of pentavalent antimony are anorexia, vomiting, nausea, malaise, arthralgia and myalgia, headache, lethargy, and pancreatitis. ECG changes are dose-dependent and most commonly include T-wave inversion and prolonged QT interval. Renal damage is a rarely reported toxic effect. Pentavalent antimony is usually well tolerated. Serious side-effects when they occur usually involve the liver or the heart when it is prudent to interrupt the course temporarily.

Breast feeding: The amount of antimony distributed into the breast milk of a patient given sodium stibogluconate was considered not to constitute a hazard and oral absorption was not detected in an animal study.1 The American Academy of Pediatrics also considers that the use of antimony is usually compatible with breast feeding.2 Others, however, have felt that more safety evaluation was required before antimony could be considered completely safe during breast feeding.
### Table 13–01 Comparison of vehicles

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Effect</th>
<th>Indications</th>
<th>Comments</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>ointments</td>
<td>occlusive and lubricating</td>
<td>dry, scaly skin</td>
<td>better topical penetration of incorporated drugs than creams and lotions; greasy, difficult to wash off; may cause folliculitis</td>
<td>soft paraffin, lanolin</td>
</tr>
<tr>
<td>creams</td>
<td>cooling and lubricating</td>
<td>moist or dry skin; use where a washable (non-greasy) and cosmetically elegant vehicle is needed</td>
<td>preservatives can cause sensitisation</td>
<td>cetomacrogol cream, aqueous cream</td>
</tr>
<tr>
<td>lotions and solutions</td>
<td>drying and cooling</td>
<td>hairy and intertriginous regions; acute exudation</td>
<td>can be applied without friction</td>
<td>calamine lotion, potassium permanganate solution</td>
</tr>
<tr>
<td>pastes</td>
<td>drying and protective</td>
<td>psoriasis, warts</td>
<td>more occlusive and absorptive, less greasy than ointments, reducing spreading of active ingredient</td>
<td>Lassar's paste (zinc oxide and salicylic acid), Upton's paste (salicylic acid and trichloracetic acid)</td>
</tr>
<tr>
<td>aerosols and sprays</td>
<td>cooling</td>
<td>conditions in which direct application is difficult or painful</td>
<td>allow application without touching skin</td>
<td>antifungals, eg miconazole sprays, sunscreen spray for hairy areas</td>
</tr>
</tbody>
</table>

### Table 13–02 Suggested weekly quantities of topical preparations

<table>
<thead>
<tr>
<th>Age</th>
<th>Face &amp; neck</th>
<th>Arm &amp; hand</th>
<th>Leg &amp; foot</th>
<th>Trunk (front)</th>
<th>Trunk (back incl. buttocks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–6 months</td>
<td>7 g</td>
<td>7 g</td>
<td>10 g</td>
<td>7 g</td>
<td>10 g</td>
</tr>
<tr>
<td>1–2 years</td>
<td>10 g</td>
<td>10 g</td>
<td>15 g</td>
<td>15 g</td>
<td>20 g</td>
</tr>
<tr>
<td>3–5 years</td>
<td>10 g</td>
<td>15 g</td>
<td>20 g</td>
<td>20 g</td>
<td>25 g</td>
</tr>
<tr>
<td>6–10 years</td>
<td>15 g</td>
<td>20 g</td>
<td>30 g</td>
<td>25 g</td>
<td>35 g</td>
</tr>
<tr>
<td>Adult &amp; child &gt;10 years</td>
<td>20 g</td>
<td>30 g</td>
<td>55 g</td>
<td>50 g</td>
<td>50 g</td>
</tr>
</tbody>
</table>

Based on twice a day application for 1 week; for corticosteroids, calcipotriol and pimecrolimus do not exceed the suggestions without specialist recommendation

### Table 13–03 Comparison of potency and uses of topical corticosteroids

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Examples of indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td></td>
</tr>
<tr>
<td>hydrocortisone (0.5–1%)</td>
<td>facial and flexural dermatitis and psoriasis; nappy dermatitis</td>
</tr>
<tr>
<td>hydrocortisone acetate (0.5–1%)</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td></td>
</tr>
<tr>
<td>betamethasone valerate (0.02 &amp; 0.05%)</td>
<td>mild-to-moderate atopic dermatitis, adjunctive treatment in extensive psoriasis</td>
</tr>
<tr>
<td>triamcinolone acetonide (0.02%)</td>
<td></td>
</tr>
<tr>
<td>desonide (0.05%)</td>
<td></td>
</tr>
<tr>
<td>Potent</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Betamethasone dipropionate (0.05%)</td>
<td>Short term use in severe inflammatory dermatoses</td>
</tr>
<tr>
<td>Betamethasone valerate (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Mometasone furoate (0.1%)</td>
<td>More severe conditions, e.g., discoid eczema</td>
</tr>
<tr>
<td>Methylprednisolone aceponate (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Very potent</td>
<td></td>
</tr>
<tr>
<td>Betamethasone dipropionate in an optimised vehicle (0.05%)</td>
<td>Severe eczema and psoriasis, e.g., refractory lichen simplex chronicus; also useful for eczema of hands and feet, occlusion may be used but atrophy may occur</td>
</tr>
</tbody>
</table>
CHAPTER 15 ANAESTHETICS

15.01. GENERAL ANAESTHESIA

15.01.01 INHALATIONAL ANAESTHETICS

HALOTHANE
ISOFLURANE
NITROUS OXIDE
SEVOFLURANE

These are liquids at room temperature, apart from nitrous oxide which is a gas. Their anaesthetic effect is directly proportional to the partial pressure of the drug in the brain. Factors that shorten induction time include: high inspired concentration, increased alveolar ventilation, reduced cardiac output, low blood gas solubility and increased alveolar-to-capillary partial pressure difference.

The rate of recovery from anaesthesia is increased with increased alveolar ventilation, increased cardiac output and low blood-gas solubility.

Mode of action
Thought to enhance inhibitory ion channel activity and inhibit excitatory activity in the brain to induce hypnosis and amnesia, and in the spinal cord to cause immobility in response to painful stimuli.

Indications
Induction and/or maintenance of general anaesthesia (desflurane: maintenance only, nitrous oxide: adjunct only).

Contraindications
Susceptibility to malignant hyperthermia (except nitrous oxide).

Specific considerations
Conditions of mouth, jaw and neck causing difficulty in airway maintenance: inability to secure airway will lead to prolonged anoxia; use only if able to maintain airway.
Full stomach or conditions predisposing to airway soiling: use measures to protect airway.
Increased intracranial pressure: may be increased further.
Cardiovascular compromise (eg hypotension, hypovolaemia): symptoms may worsen; correct before administration if possible; reduce dose and use cautiously.
Conditions where cardiac output cannot be increased (eg constrictive pericarditis, stenotic valvular disease, heart failure)—vasodilation due to anaesthetic cannot be compensated by increasing cardiac output; reduce dose and use cautiously.
Coronary heart disease—risk of myocardial ischaemia if hemodynamic instability occurs.
Myasthenia gravis—muscle weakness may increase; adjust dose of anticholinesterase treatment if necessary.
Muscular dystrophies—volatile agents may precipitate life-threatening rhabdomyolysis; use alternative anaesthetic agents.
Addison's disease or myxedema—hypnotic effect may be prolonged or potentiated.
Debilitated patients—more sensitive to adverse and anaesthetic effects; reduce dose and monitor closely.
Elderly: With increasing age, lower concentrations of inhalational agents are usually required.
Children: Increased concentrations of inhalational agents are usually required in neonates and infants.

Adverse effects
All volatile agents can trigger malignant hyperthermia.
Most other adverse effects are mild or moderate in severity, dose-dependent and result from pharmacological effects (eg hypotension, bradycardia, tachycardia, or respiratory depression).
Common: shivering (independent of temperature), nausea, vomiting.
Infrequent: arrhythmias.
Rare: malignant hyperthermia (volatile agents).

Comparative information
See also Table 15.01 Comparison of inhalational anaesthetics

Delivery: Desflurane requires a modified heated vaporiser. The other volatile agents can be delivered by conventional vaporisers. Nitrous oxide is supplied via hospital pipelines or from metal cylinders.
Respiratory effects: All cause a dose-related depression of tidal volume and of the respiratory response to hypercapnia and hypoxaemia. They are also effective bronchodilators.
Cardiovascular effects: Some cardiovascular effects of volatile agents are antagonized by the modest hypercapnia which occurs during spontaneous ventilation, and by adding nitrous oxide (also allows use of lower concentrations of volatile agents).
Nitrous oxide causes a direct depressant but also a sympathomimetic effect on the myocardium, resulting in minimal change in fit patients; myocardial depression may occur when the sympathomimetic effect is blocked by opioids or in the presence of myocardial ischaemia.

There is growing evidence that isoflurane and sevoflurane have myocardial protective properties and are among the agents of choice in coronary heart disease.

Nervous system effects: While all the inhalational agents cause a dose-dependent increase in cerebral blood flow, this effect is more marked with nitrous oxide. Low concentrations of the other agents may be used in neuroanaesthesia, unless the intracranial pressure is significantly raised.

Hepatotoxicity: The likelihood of immune hepatitis developing after exposure to a volatile anaesthetic depends on the amount of trifluoroacetic acid (TFA) produced during its metabolism; this is less with desflurane and isoflurane than with halothane (no longer available). TFA is not a metabolite of sevoflurane.

**Administration instructions**

To prevent hypoxia, give inhalational agents with concentrations of oxygen greater than that in air.

Administer volatile agents via calibrated, agent-specific vaporisers using oxygen with or without air or nitrous oxide as the carrier gas. Do not use >1 volatile agent at a time.

Use with a scavenging system and/or effective ventilation to avoid accidental inhalation or occupational exposure.

**Patient counselling**

For short-stay surgery:

- a responsible person must be available to take you home and look after you
- do not drive, operate machinery or engage in other hazardous activities for 24 hours or more (depending on the doses and drugs used) after anaesthesia
- do not consume alcohol during this period.

**Practice points**

- in general, concentrations of volatile agents required for anaesthesia are:
  - lower in increasing age, pregnancy, hypothermia, hypothyroidism and with drugs such as nitrous oxide and CNS depressants including opioids
  - higher in neonates and infants, hyperthyroidism, pyrexia and with CNS stimulants such as ephedrine and amphetamine
- concentration of volatile agent can be reduced by using nitrous oxide as an adjunct
- the risk of postoperative nausea and vomiting is increased with the use of inhalational agents, particularly nitrous oxide; avoid in high risk patients if possible
- there is a risk of extreme heat or fire, and a risk of carbon monoxide production in the breathing circuit of anaesthetic machines when volatile agents are used with a desiccated carbon dioxide absorbent

**HALOTHANE**

**Mode of action**

Halothane is a volatile liquid anaesthetic. It’s advantages are that it is potent, induction is smooth, pleasant to inhale, the vapor is not irritant to the skin and mucous membranes and does not produce necrosis when split on tissues. It suppresses salivary, mucous, bronchial, and gastric secretions and dilates the bronchioles.

**Indications**

Induction but more often for the maintenance of general anaesthesia.

**Specific considerations**

Halothane reduces muscle tone in pregnant uterus and generally its use is not recommended in obstetrics because of the increased risk of postpartum hemorrhage.

Halothane should not be used for patients with cardiac arrhythmias.

Halothane was considered to be unsafe in patients with acute porphyria.

**Adverse Effects**

Cardiovascular: Halothane has a depressant action on the cardiovascular system and reduces blood pressure; signs of overdosage are bradycardia and profound hypotension. It is also a respiratory depressant and can cause cardiac arrhythmias; there have been instances of cardiac arrest. The sensitivity of the heart to sympathomimetic amines is increased.

Hepatic: dysfunction, hepatitis, and necrosis have been reported following the use of halothane, more frequent following repeated use. Serious hepatotoxicity has limited its use in recent years.

Other: malignant hyperpyrexia, involuntary muscle movements, hiccup, coughing, bronchospasm, laryngospasm and respiratory depression.

**Drug interactions**
1. Adrenaline: the concurrent use of adrenaline with halothane may lead to serious side effects since fatalities have been reported in some patients associated with ventricular fibrillation.
2. Calcium-Channel Blockers: verapamil has been reported to cause cardiac arrest when given with halothane.
3. Morphine, chlorpromazine: both drugs increase the depressant effects of halothane.
4. Suxamethonium: reports of potentiation of suxamethonium-induced muscle damage by prior anaesthetic induction using halothane have been observed.

Sodium Bicarbonate: sodium bicarbonate, given to induce metabolic alkalosis, decreased total peripheral resistance during halothane anaesthesia and might lead to severe hypotension.

**Dosage**
Anaesthesia may be induced with 2 to 4% v/v of halothane in oxygen or mixtures of nitrous oxide and oxygen; It takes up to about 5 minutes to attain surgical anaesthesia and halothane produces little or no excitement in the induction period. For induction in children a concentration of 1.5 to 2% v/v has been used. The more usual practice is to induce anaesthesia with an intravenous agent. Anaesthesia is maintained with concentrations of 0.5 to 2% v/v depending on the flow rate used; the lower concentration is usually suitable for the elderly.

**Products**
HALOTHANE LIQUID 250 ML BOTTLE (ANESTANE®, HALOTHANE ®)

**ISOFLURANE**

**Mode of action**
Thought to enhance inhibitory ion channel activity and inhibit excitatory activity in the brain to induce hypnosis and amnesia, and in the spinal cord to cause immobility in response to painful stimuli.

**Indications**
Induction and maintenance of general anaesthesia.

**Contraindications**

**Specific considerations**

Pregnancy: Limited data; ADEC category B3. Reduce maintenance dose in obstetric anaesthesia.
Breastfeeding: No data.

**Adverse effects**
Common: On induction, coughing, breath-holding, laryngospasm

**Dosage**
Induction: 1.5–3% inspired concentration in oxygen and nitrous oxide produces surgical anaesthesia within 10 minutes; alternatively, start at an inspired concentration of 0.5% and increase gradually to the required level.
Maintenance: 0.5–2.5% inspired concentration in oxygen and nitrous oxide; 1.5–3.5% inspired concentration when used with oxygen alone.

**Practice points**
- although isoflurane is marketed for induction of anaesthesia, it is irritant to the airway, and can cause coughing, laryngospasm and breath-holding

**Products**
ISOFLURANE 100 % LIQUID 100 ML BOTTLE (FLORAN®, ISOFURANE®)

**NITROUS OXIDE**

**Mode of action**
Nitrous oxide is an anesthetic administered by inhalation. It is a weak anaesthetic with minimum alveolar concentration value of 110%. It has strong analgesic properties, but produces little muscle relaxation.

**Indications**
Nitrous oxide is used as an adjuvant to other anaesthetics and permits them to be used at a significantly reduced dosage. It is given with oxygen for anaesthesia especially in obstetrics. Recovery is usually rapid from nitrous oxide anaesthesia.

**Specific considerations**
Air-containing cavities (e.g. middle ear occlusion, abdominal distension, pneumothorax, air embolus), or during or after pneumoencephalography or vitreoretinal surgery involving gases such as sulphur hexafluoride: risk of increased pressure and/or volume within such cavities.
Vitamin B12 deficiency: increased risk of neurological dysfunction, including subacute combined degeneration of the spinal cord with prolonged exposure.
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: No data.
Adverse effects
The main complications are those due to varying degrees of hypoxia.
Rare: With prolonged (eg >24 hours) or repeated use: megaloblastic anaemia, leucopenia, agranulocytosis, neuropathy, myeloneuropathy.

Dosage
Induction: 70% with 30% oxygen, (in combination with other anaesthetic agent).
Maintenance: 30–70% with oxygen, (in combination with other anaesthetic agent).
Analgesia: 25–50% with oxygen.

Practice points
- in anaesthesia, it is mainly used as an adjunct to other inhalational anaesthetics, allowing them to be used at lower concentrations
- it is a weak anaesthetic but has strong analgesic properties; used in subanaesthetic concentrations in obstetrics, emergency care and procedures not requiring loss of consciousness; premixed nitrous oxide 50% and oxygen 50% alone is suitable for self-administration
- prolonged inhalation can inactivate vitamin B₁₂ and interfere with DNA synthesis causing haematological and neurological adverse effects; avoid exposures of >6 hours
- whether or not chronic low level occupational exposure is harmful to staff remains unresolved; control nitrous oxide pollution using a scavenging system and effective ventilation
- protect cylinders containing 50% nitrous oxide and 50% oxygen from the cold; if cooled to temperatures < −7°C, liquid nitrous oxide separates and may require remixing before use

Products
NITROUS OXIDE LIQUID 50-70 % IN CYLINDERS (DIFFERENT COMPANIES)

SEVOFLURANE
See under Isoflurane

Dosage
Induction: Up to 8% inspired concentration in oxygen with or without nitrous oxide produces surgical anaesthesia in <2 minutes.
Maintenance: 0.5–3% inspired concentration in oxygen with or without nitrous oxide; use concentrations in lower end of range when using nitrous oxide.

Practice points
- used widely for induction in children as is not irritant to the airway and has good cardiovascular stability
- apnea can occur with prolonged use of high concentrations; use for a brief time only
- emergence times are usually short following sevoflurane anaesthesia (unless administration is prolonged); ensure adequate analgesia is given to cover the early recovery period
- agitation during recovery appears to be common in children
- there is a theoretical risk of nephrotoxicity due to Compound A which is formed by the breakdown of sevoflurane by carbon dioxide absorbents; reduce sevoflurane degradation by avoiding prolonged use in low-flow systems (<2 L/minute)

Products
SEVOFLURANE LIQUID 250 ML BOTTLE (SEVOFLORANE®)

15.01.02 INTRAVENOUS ANAESTHETICS
EDROPHONIUM
KETAMINE
MIDAZOLAM
PROPOFOL
THIOPENTAL

In appropriate doses, IV general anaesthetic drugs produce rapid, reversible loss of consciousness and insensibility to surgical stimuli within 1 arm-brain circulation time.
After a single dose, the anaesthetic effect is terminated predominantly by redistribution of the drug from the brain back into the blood. If metabolism is rapid, it may contribute to recovery of consciousness.

Indications
Induction and maintenance of anaesthesia.
Conscious sedation (midazolam; propofol in adults).
Sedation during ventilation (midazolam; propofol in adults).

Specific considerations
Cardiovascular compromise (eg hypotension, hypovolaemia): may worsen symptoms; correct before administration if possible; reduce dose and use cautiously.
Conditions where cardiac output cannot be increased (eg constrictive pericarditis, stenotic valvular disease, heart failure): anaesthetic-induced vasodilatation cannot be compensated for; reduce dose and use cautiously.
Conditions of mouth, jaw and neck causing difficulty in airway maintenance—inability to secure airway will lead to prolonged anoxia; use only if airway secured.
Risk factors for aspiration—use measures to protect airway.
Addison's disease, severe anaemia or myxedema—hypnotic effect may be prolonged or potentiated.
Debilitated patients—more sensitive to adverse and anaesthetic effects; reduce dose and monitor closely.
Elderly: More sensitive to anaesthetic effects; reduce dose and monitor closely.

Comparative information
All the IV anaesthetic agents, except ketamine, cause dose-related respiratory, laryngeal reflex and cardiovascular depression. A period of apnea frequently follows induction, and is succeeded by slow and shallow breathing. BP decreases because of myocardial depression and peripheral vasodilatation.
Thiopentone produces the most rapid onset of anaesthesia, but recovery is slower than with propofol (metabolised approximately 10 times faster than thiopentone and has less of a hangover sensation). Minor stimuli can cause laryngospasm during light thiopentone anaesthesia.
Propofol is most effective at suppressing pharyngeal and laryngeal reflexes allowing rapid control of the airway, including insertion of laryngeal mask and endotracheal intubation.
Propofol has a greater incidence of hypotension and pain on injection than the other IV agents. It has some antiemetic effect and causes less postoperative nausea and vomiting when used alone.
Midazolam is the least effective IV agent for induction of anaesthesia, but its anterograde amnesic effect may be useful.
Ketamine is a potent analgesic at subanaesthetic concentrations; the other agents do not have analgesic properties and addition of opioids is usually necessary. It can be administered IM as well as IV.
Ketamine can cause cardiovascular and respiratory stimulation at recommended doses. It maintains pharyngeal and laryngeal reflexes compared with other IV anaesthetic agents, but this is not guaranteed and the usual precautions must be taken to prevent aspiration.
Recovery from ketamine is prolonged compared with other IV agents; emergence reactions may occur.

Administration instructions
Inject slowly (usually over 30–90 seconds), particularly in elderly or debilitated patients, and titrate to effect while monitoring the patient continuously.

Patient counselling
For short-stay surgery:
- a responsible person must be available to take you home and look after you
- do not drive, operate machinery or engage in other hazardous activities for 24 hours or more (depending on the doses and drugs used) after anaesthesia
- do not drink alcohol during this period.

Practice points
Response to IV anaesthetics varies widely; required dose may be lower or higher than recommended range; titrate to response.
- higher induction doses may be required in patients with acquired tolerance to sedatives, hypnotics, opioids or alcohol
- a small dose of short acting opioid improves the smoothness of induction and reduces the dose required; however, it potentiates respiratory depression
- induction can be followed by maintenance of anaesthesia with further doses or IV infusion of the same drug, or with inhalational anaesthetic agents.

EDROPHONIUM
Mode of action
Reduces breakdown of neurally released acetylcholine by inhibiting cholinesterase; enhances neuromuscular transmission in skeletal and smooth muscles.
**Indications**
Myasthenia gravis.
Reversal of neuromuscular blockade induced by non-depolarising neuromuscular blockers.

**Contraindications**
Intestinal or urinary obstruction.

**Specific considerations**
Asthma, cardiovascular disorders (including arrhythmia, bradycardia, hypotension, coronary heart disease), seizures, Parkinson's disease, peptic ulcer: risk of aggravation.
Renal impairment: Requires dose reduction.
Pregnancy: Seek specialist advice; Manufacturer advises use only if potential benefit outweighs risk.
Breastfeeding: Safe to use; monitor infant for muscular weakness.

**Adverse effects**
Common: increased salivation, nausea, vomiting, diarrhea, abdominal cramps.
Infrequent: rash, anaphylaxis.
Overtreatment: May lead to a cholinergic crisis with increased cholinergic effects (e.g., excessive sweating, involuntary defecation and urination, miosis, nystagmus, bradycardia, hypotension, increased muscle weakness leading to fasciculation and paralysis), CNS effects (e.g., ataxia, seizures, agitation, coma) and death due to respiratory failure or cardiac arrest.

Distinction between a cholinergic crisis (overtreatment) and a myasthenic crisis (undertreatment) may be difficult (especially if an anticholinergic drug is used to relieve adverse effects), and may require an edrophonium test.

**Dosage**
Brief reversal of non-depolarising neuromuscular blockade: by intravenous injection over several minutes, 500-700 micrograms/kg (after or with atropine sulphate 600 micrograms)
The usual diagnostic procedure is to inject 2 mg intravenously and, if no adverse reaction occurs within 30 to 45 seconds, to continue with the injection of a further 8 mg. The recommended total dose for children is 100 micrograms/kg, one-fifth of the dose being given initially, followed 30 seconds later by the remainder if no adverse effects develop.

When intravenous injection is difficult edrophonium chloride may be given by intramuscular injection; the usual dose in adults is 10 mg while children below 34 kg in weight may be given 2 mg and heavier children 5 mg; a suggested dose for infants is 0.5 to 1 mg given intramuscularly or subcutaneously.
Atropine should always be available when the test is carried out in order to treat any severe muscarinic reactions that may occur.
To detect under- or over-treatment, test doses of 1 to 2 mg of edrophonium chloride are given intravenously to distinguish severe symptoms of myasthenia gravis due to inadequate therapy from the effects of overdosage with anticholinesterase drugs. If treatment has been inadequate, edrophonium chloride will produce an immediate amelioration of symptoms, whereas in cholinergic crises due to over-treatment the symptoms will be temporarily aggravated.

**Practice points**
- atropine (0.25 mg SC/IM) or oral propantheline may be necessary to minimize muscarinic adverse effects at the beginning of treatment, but should not be given routinely because they may mask signs of overtreatment
- transient resistance may occur after prolonged treatment; decrease dosage or withdraw drug for several days under medical supervision.

**Products**
EDROPHONIUM AMPS 10 MG/AMP (AS HCL) (NOT REGISTERED)

**KETAMINE**

**Mode of action**
Antagonises N-methyl-D-aspartate (NMDA) receptors; also interacts with muscarinic receptors, descending monoaminergic pain pathways, voltage-sensitive calcium channels and opioid receptors in brain and spinal cord.

**Indications**
Marketed: Induction and maintenance of anaesthesia.
Accepted: Pain relief.

**Contraindications**
Allergy to ketamine.
Conditions which may be worsened by an increase in BP and/or heart rate (e.g., poorly controlled hypertension, stroke, intracerebral hemorrhage, angina, recent MI, stenotic valvular heart disease).
Specific considerations
Psychiatric disorders: hallucinations, irrational behaviour and other effects may occur; avoid use.
Raised intracranial or intraocular pressure: may be further raised; avoid use.
Penetrating eye injury: risk of loss of intraocular contents; avoid use.
Tachyarrhythmias, chronic heart failure, hyperthyroidism—may worsen (ketamine increases BP and heart rate); avoid use.
Pregnancy: Safe to use; ADEC category A.
Breastfeeding: Limited data; avoid use.

Adverse effects
Common: raised BP and pulse rate, increased muscle tone (sometimes tonic-clonic and resembling seizures), lacrimation, hypersalivation, raised intracranial pressure, raised intraocular pressure, emergence reactions
Infrequent: diplopia, nystagmus, postoperative nausea and vomiting, hypotension and bradycardia, pain on injection, erythema, morbilliform rash.
Rare: apnea, laryngospasm, arrhythmias, anaphylaxis.

Emergence reactions
May occur during recovery and for up to 24 hours. They include vivid (possibly unpleasant) dreams, restlessness, confusion, hallucinations and irrational behaviour. Less common in children, the elderly and after IM administration, and are reduced by benzodiazepine premedication and by minimising stimulation during the recovery period.
Treatment with a small dose of thiopentone or a benzodiazepine may be necessary for severe reactions.
Rarely, recurrences of emergence reactions can occur days or weeks after drug exposure.

Dosage
Induction
IV, 1–4.5 mg/kg; usually 2 mg/kg over 60 seconds provides anaesthesia within 30 seconds lasting for 5–10 minutes.
IM, 6.5–13 mg/kg; usually 10 mg/kg provides anaesthesia within 3–4 minutes lasting for 12–25 minutes.
IV infusion, 0.5–2 mg/kg initially then infuse at 10–45 micrograms/kg/minute; adjust according to response.

Maintenance
IV, increments of half to full dose repeated as required.

Analgesia for painful procedures
When used as sole agent and supervised by anaesthetist:
IV, up to 1–1.5 mg/kg slowly over 2–5 minutes, titrated to effect; give half dose every 10 minutes if required for prolonged procedures.
IM, 4–5 mg/kg; repeat after 10 minutes if required for prolonged procedures.

Administration instructions
Dilute dose with an equal volume of water for injection, sodium chloride 0.9% or glucose 5% before IV injection.
Give IV slowly; rapid administration may result in respiratory depression and enhanced hypertensive response.

Practice points
- low dose SC/IV ketamine is used with other analgesic drugs for pain relief, particularly neuropathic pain; seek specialist advice
- premedication with an anticholinergic to reduce secretions is recommended before its use in anaesthesia
- after a single dose, analgesic effects last about 40 minutes and amnesia lasts 1–2 hours
- time for complete recovery may be several hours and increases with increasing dose
- the rise in systolic BP after IV injection is usually 20–25% of preanaesthetic values, with the peak after approximately 5 minutes and a return to normal over next 10–20 minutes
- transient apnea may occur after IV injection, but ventilation is well maintained and even slightly increased thereafter, unless high doses are given
- ketamine maintains pharyngeal and laryngeal reflexes compared with other IV anaesthetic agents, but this is not guaranteed and the usual precautions must be taken to prevent aspiration
- useful in reactive airways disease since it reduces airways resistance
- bioavailability by the IM route is >90%
- useful as sole agent for short painful procedures, such as ocular examination in children, changing wound and burn dressings, especially as there is minimal delay in resuming eating
- illicit/recreational use of ketamine occurs (known as 'special K' or 'vitamin K'); subhypnotic doses cause a dissociated out of body/near death experience, possibly with hallucinations
MIDAZOLAM

Mode of action
Potentiates the inhibitory effects of gamma-aminobutyric acid (GABA) throughout the CNS, resulting in anxiolytic, sedative, hypnotic, anterograde amnesic, muscle relaxant and antiepileptic effects.

Indications
Premedication: 20 to 30 minutes before induction and anaesthesia, alone or in combination with anticholinergic and possibly analgesic drugs.
Induction of anaesthesia in children: combination of sleep and anaesthesia with ketamine (ataralgesia).

Contraindications
Allergy to benzodiazepines.

Specific considerations
Respiratory disease, sleep apnea: compromised respiratory drive may result in hypoventilation and hypoxaemia; use cautiously.
Muscle weakness: risk of exacerbation; use cautiously.
Myasthenia gravis, muscular dystrophies and myotonias: respiratory depression prolonged or potentiated; reduce dose.
Renal impairment: Increased sensitivity to CNS effects; reduce dose in severe impairment.
Hepatic impairment: Increased sensitivity to CNS effects; avoid in severe impairment as can precipitate coma.
Elderly: Increased risk of oversedation, ataxia, confusion, falls, respiratory depression and short term memory impairment; reduce dose and monitor closely.
Children: When used as oral premedication, paradoxical excitation and an increased incidence of emergence delirium may occur.
Pregnancy: Avoid use if possible; high doses before or during labour may cause floppy infant syndrome (hypotonia, lethargy and poor suckling); ADEC category C.
Lactation: Limited data; highly protein bound, short half-life, feed as usual after surgery.

Coexisting conditions
Cardiovascular compromise (eg hypotension, hypovolaemia): may exacerbate symptoms; resuscitate patient before administration if possible; reduce dose and use cautiously.
Conditions where cardiac output cannot be increased (eg constrictive pericarditis, stenotic valvular disease, heart failure): vasodilation cannot be compensated by increasing cardiac output; reduce dose and use cautiously.
Conditions of mouth, jaw and neck causing difficulty in airway maintenance: inability to secure airway will lead to prolonged anoxia; use only if airway secured.
Addison's disease, severe anaemia or myxedema: hypnotic effect may be prolonged or potentiated.
Debilitated patients: more sensitive to adverse and anaesthetic effects; reduce dose and monitor closely.
Elderly: More sensitive to anaesthetic effects; reduce dose and monitor closely.

Adverse effects
Common: following injection: pain on injection, hypotension, hiccup, cough.
Infrequent: following injection: thrombophlebitis, erythema, rash, laryngospasm, bronchospasm, headache, nausea, vomiting, confusion, restlessness.
Rare: cardiac arrhythmias, cardiorespiratory arrest, anaphylactic/anaphylactoid reactions.

Dosage
When used as sole agent:
Adult
Conscious sedation, IV, usual dose 2–2.5 mg; if elderly or debilitated, reduce initial dose to 1–1.5 mg. Give further 1 mg doses as needed; doses >5 mg rarely needed.
Induction of anaesthesia, IV 0.15–0.35 mg/kg at a rate of approximately 2.5 mg every 10 seconds
Sedation (intensive care), IV 0.03–0.2 mg/kg/hour
Premedication, IM 0.07–0.08 mg/kg 1 hour before surgery. Elderly/debilitated, IM 0.02–0.05 mg/kg
Acute behavioural disturbance, IM 5 mg or 0.1 mg/kg in patients <50 kg.
Child
Induction of anaesthesia, IV 0.15–0.5 mg/kg; doses >0.3 mg/kg rarely needed.
Sedation in intensive care units, IV 0.03–0.3 mg/kg initially, then 0.5–4 microgram/kg/minute.
Premedication, oral 0.4–0.6 mg/kg (maximum 15 mg), or intranasal 0.2–0.4 mg/kg (maximum 10 mg).
Renal impairment: Halve dose in severe renal impairment.

Administrative instructions
Individualise dose and administer slowly. The onset of the clinical effect may be delayed and there is a danger of overdosage if it is given rapidly without waiting to assess its effects.
Dilution with sodium chloride 0.9% or glucose 5% facilitates slower IV injection.
For sedation, give the initial dose and wait 3 or more minutes to evaluate the clinical effect before titrating each additional increment. The end point for sedation is drowsiness and slurring of speech; check that the level of consciousness is not deteriorating by ensuring that the patient can respond to verbal stimulus.

Practice points
- the onset of sedation after IM injection is 15 minutes, peak sedation occurs after 30–60 minutes; following IV injection, maximum sedation occurs after 2–3 minutes
- following IM administration, the bioavailability is >90%
- respiratory depression, apnea, cardiovascular depression and cardiac arrest are more likely after IV injection, but can also occur after IM administration; monitor closely; flumazenil may be used as a reversal agent
- time to recovery is dose dependent; onset of sedation is not
- induction of anaesthesia is unsuccessful in approximately 14% of patients with midazolam alone, but in only about 1% when given with an opioid
- it does not prevent the increase in heart rate and/or BP or the rise in intracranial pressure associated with endotracheal intubation
- may be used for its amnesic effect during induction of anaesthesia
- anterograde amnesia may last longer than sedation; advise the patients and their carers
- a gradual reduction in dose is recommended after prolonged IV administration of midazolam; abruptly stopping may lead to withdrawal symptoms.

Products
MIDAZOLAM AMPS 15 MG/AMP (AS HCL) 3 ML AMP (DALAM®, DORMICUM®, HIKMA MIDAZOLAM®)

PROPOFOL
Mode of action
Exact mechanism of action is uncertain, but its main depressant CNS action is thought to be mediated by interaction with the gamma-aminobutyric acid (GABA) receptor at a site different to that of barbiturates and benzodiazepines. Other probable modes of action include shortening of channel opening times at nicotinic acetylcholine receptors and sodium channels in the cerebral cortex. The vasodilation associated with propofol may be the result of its interaction with lysophosphatide which causes vasoconstriction.

Indications
Induction and maintenance of anaesthesia in adults and children >3 years.
Sedation of ventilated adults.
Conscious sedation in adults.
Induction and maintenance of anaesthesia

Contraindications
Allergy to propofol, soya oil, egg lecithin.

Specific considerations
Severe respiratory compromise: further respiratory depression occurs; consider alternatives, including ketamine.
Myasthenia gravis, muscular dystrophies and myotonias: respiratory depression prolonged or potentiated; reduce dose.
Raised intracranial pressure (eg during neurosurgery): cerebral protective effects may be lost with systemic hypotension and reduced cerebral perfusion; monitor carefully.
Obstetric anaesthesia: may be associated with neonatal depression; avoid use.
Hyperlipidaemia, fat metabolism disorders: increases in serum triglyceride concentration may occur when propofol is given for prolonged periods (>24 hours); monitor closely and reduce quantity of concurrently administered lipids if necessary.
Children: Compared to adults, larger induction and maintenance doses are required because of the greater volume of distribution and higher total body clearance. Not recommended for intensive care sedation or conscious sedation in children.
Pregnancy: May be associated with neonatal depression; ADEC category C.
Lactation: Appears safe.

Adverse effects
Common: pain on injection, bradycardia, hypotension, apnea, flushed skin or rash, cough, excitation at induction (involuntary movements, including twitches, tremors, hypertonus and hiccups).
Infrequent: cardiac arrhythmias.
Rare: anaphylactic/anaphylactoid reactions, thrombosis and phlebitis at injection site, seizure, fever
Continuous sedation in children.
Lactic acidosis, bradyarrhythmias, progressive myocardial failure, fatty liver and death have occurred with prolonged use in intensive care.

Dosage
Presented as a 1% preparation (10 mg/mL).
Anaesthesia
Induction
Healthy, age 9–55 years, IV 2–2.5 mg/kg, titrate to response over 30–60 seconds.
Healthy child 3–8 years, IV 2.5–3.5 mg/kg, titrate to response over 30–60 seconds.
Age >55 years or debilitated and age 3–55 years, IV 1–1.5 mg/kg, titrate to response over 30–90 seconds.
Maintenance
Adult, IV infusion 4–12 mg/kg/hour.
Child 3 years and over, IV infusion 7.5–15 mg/kg/hour.
Adult, child 3 years and over, IV bolus 25–50 mg as required.
Sedation during ventilation
Adult, IV infusion 1–3 mg/kg every hour, increased as required.
Conscious sedation
Adult, IV 0.5–1 mg/kg over 1–5 minutes, then infuse 1.5–3 mg/kg/hour. A bolus of 10–20 mg may be given if a rapid increase of sedation is required (less in debilitated and those >55 years).

Administration instructions
Inject bolus dose over 30–60 seconds or more slowly if patient is elderly or debilitated.

Practice points
- unconsciousness occurs approximately 30 seconds (longer in older or debilitated patients) after injection; recovery from induction dose usually occurs within 5–10 minutes
- pain on injection may be reduced by giving 0.5 mg/kg lignocaine IV (preferably with a tourniquet) 30–120 seconds before injecting propofol
- cardiovascular effects of propofol are related to peak arterial concentration which in turn depends on the rate of administration; minimize the extent and duration of cardiovascular depression by reducing the injection rate or using an infusion rather than a bolus dose
- bradycardia and asystole may occur as propofol does not have vagolytic activity; in addition, hypotension after induction is not compensated by tachycardia
- the incidence of involuntary movements is 15–75%, and can occur at any time during anaesthesia
- although propofol appears to have some antiemetic effect, it is not more effective than other antiemetics
- physically incompatible with atracurium or mivacurium; flush IV cannula with sodium chloride 0.9% before injecting
- strictly adhere to aseptic technique; it is a single-use product as the formulation is a good medium for bacterial growth
- 1 mL of propofol provides 0.1 mg of lipid (1.1 kcal); monitor plasma lipid if used continuously for >3 days
- used by specialist anaesthetists in children <3 years old for induction of anaesthesia and occasionally for short term sedation during procedural work.

Products
PROPOFOL AMPS 1 % 20 ML AMP (PROPOFOL®, SAFOL®, DIPRIVAN®, RECOFOL®, PROVIVE®)
PROPOFOL AMPS 1 % 50 ML AMP (SAFOL®, RECOFOL®)

THIOPENTAL
Mode of action
Potentiates action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at multiple sites in the CNS, resulting in sedative, hypnotic, anaesthetic, and anticonvulsant effects. It also depresses the actions of excitatory neurotransmitters in the CNS.
**Indications**
Marketed: Short surgical procedures; sole agent, Induction of general anaesthesia, Seizures; short term control (critical care areas only).
Accepted: Cerebral protection (e.g. neurosurgery), Raised intracranial pressure.

**Contraindications**
Allergy to barbiturates.
Porphyria.

**Specific considerations**
Asthma: bronchospasm may occur; use alternative agent.
Severe respiratory compromise: further respiratory depression occurs; consider alternatives, including ketamine.
Myasthenia gravis, muscular dystrophies and myotonias: respiratory depression prolonged or potentiated; reduce dose.
Renal impairment: May need to reduce dose; administer slowly.
Hepatic impairment: Reduces metabolism and drug clearance. Decrease dose and administer slowly.
Elderly: Slower recovery of cognitive and psychomotor functions than in younger adults; lower doses are generally adequate.
Pregnancy: Safe to use; ADEC category A. If induction of anaesthesia to delivery time is short, respiratory or cardiovascular depression may occur in the neonate.
Lactation: Safe to use; small amounts excreted in breast milk.

**Adverse effects**
Common: transient erythema noted as blushing, ‘garlic’ taste sensation during induction, hypotension, respiratory and myocardial depression, prolonged somnolence with repeated doses
Infrequent: laryngospasm (during light anaesthesia), pain at injection site
Rare: anaphylaxis, bronchospasm
Injection site reactions
Extravasation may cause tissue necrosis. Treat irritant effects with local injection of procaine 2% to relieve pain and enhance vasodilation.
Intra-arterial injection causes arterial spasm, thrombosis and potentially gangrene. Treatment includes stopping injection, intra-arterial administration of local anaesthetic agent (e.g. lignocaine or procaine) and a vasodilator (e.g. papaverine 20–40 mg or phentolamine 5–10 mg), sympathetic blockade of the limb (e.g. stellate ganglion or brachial plexus block) and anticoagulation with heparin.

**Dosage**
**Induction and maintenance**
Administered as a 2.5% solution (25 mg/mL).
Adult
IV bolus, 3–4 mg/kg (higher dose required in patients with acquired tolerance to sedatives, hypnotics, opioids or alcohol); 1–2.5 mg/kg in debilitated or elderly patients.
Maintenance (sole anaesthetic agent), additional injections of 25–50 mg when needed.
Child
IV bolus, 5–6 mg/kg; neonates 2–3 mg/kg.
**Cerebral protection**
IV bolus, 1.5–3.5 mg/kg; repeat as required.
Seizure control
Adult, IV bolus 50–125 mg, given in 25 mg increments. For seizures after the use of a local anaesthetic, 125–250 mg given over a 10 minute period may be needed. If seizures continue, IV infusion may be required; seek specialist advice.
Child, IV bolus 3–5 mg/kg, then 1–4 mg/kg/hour with ventilation support.

**Administration instructions**
Inject slowly (50–75 mg every 20–40 seconds) and titrate to effect, particularly if patient is elderly or debilitated. Slow injection minimizes the possibility of overdose.

**Practice points**
- marketed for supplementation of regional anaesthesia or low potency agents (e.g. nitrous oxide), but in clinical practice it is not commonly used for this indication
- unconsciousness occurs in 10–20 seconds (longer in older or debilitated patients) after injection, with increasing depth of anaesthesia over the following 20–30 seconds; recovery occurs after 5–10 minutes, longer after repeated doses
• laryngeal reflexes are not usually depressed until deep levels of anaesthesia are reached; during light anaesthesia minor stimuli can cause laryngospasm
• thiopentone reduces cerebral metabolic rate and cerebral blood flow providing benefit in episodes of focal cerebral ischaemia (e.g., status epilepticus, severe head injury)
• flush IV cannula with sodium chloride 0.9% before injecting suxamethonium, atracurium or vecuronium to avoid precipitation
• recovery from a single dose is rapid due to redistribution; repeated doses have a cumulative effect with delayed recovery
• return to full alertness and psychomotor function takes 24 hours, longer if repeated doses given; not first choice in day surgery procedures
• thiopentone does not provide analgesia, and at low plasma concentrations may increase sensitivity to somatic pain
• potential exists for induction of liver enzymes and subsequent drug interactions if used frequently over a short period of time

Products
THIOPENTAL SODIUM VIAL 1 GM/VIAL (PENTOTHAL®, THIOPENTAL®)

15.02 NEUROMUSCULAR BLOCKERS
Neuromuscular blocking drugs produce skeletal (including respiratory) muscle relaxation which is used during general anaesthesia to:
• facilitate endotracheal intubation and hence control of the airway
• allow mechanical ventilation
• prevent reflex muscle contraction
• improve access to the surgical field.
They have no sedative or analgesic effects, and should only be used with adequate anaesthesia. Facilities for airway maintenance, including endotracheal intubation, oxygenation and ventilation must be available whenever these drugs are used.
For safest and most effective use, assess the degree of muscle relaxation by monitoring muscle twitch response to peripheral nerve stimulation.
Conditions of mouth, jaw, neck, larynx and lower airway which may cause airway obstruction or make endotracheal intubation difficult: inability to ventilate lungs will lead to prolonged anoxia; avoid use until airway secure.
Acidosis, dehydration, debilitation, electrolyte imbalance (hypokalaemia, hypermagnesaemia, hypocalcaemia): enhance effects of neuromuscular blocking drugs; where possible correct before administration, reduce dose and monitor neuromuscular blockade.
Hypothermia: increases intensity and/or duration of action of all neuromuscular blockers apart from pancuronium (effect decreased); reduce dose and monitor neuromuscular blockade.
Anaphylactoid reaction to neuromuscular blocking agents: allergic cross-reactivity has been reported; refer to specialist for skin testing for sensitivity to other neuromuscular blockers.

Adverse effects
In general, the most frequent problems are prolonged paralysis beyond the time needed for surgery, and inadequate reversal of neuromuscular blockade (varies from muscle weakness to profound paralysis resulting in respiratory insufficiency or apnea).

Comparative information
Neuromuscular blocking drugs are divided into depolarising and non-depolarising agents according to their effect at the neuromuscular junction. Suxamethonium is the only depolarising drug.
The onset and duration of action of suxamethonium is shorter than any of the other muscle relaxants; if suxamethonium is contraindicated, rocuronium can be used for rapid sequence induction, as its onset of action is only slightly slower (but longer duration of action).
The non-depolarising neuromuscular blocking agents do not cause the muscle fasciculations associated with suxamethonium.
Neostigmine reverses the action of the non-depolarising muscle relaxants, but potentiates that of suxamethonium; recovery from suxamethonium is spontaneous.

Dosage
Calculate the dosages of neuromuscular blocking agents taking into account: the anaesthetic technique, potential interactions with drugs used before and during anaesthesia, the estimated duration of the operation and the condition
of the patient. In patients >30% above their ideal weight, base the initial dose on ideal weight, rather than actual weight.

Administration instructions
Flush IV cannula with sodium chloride 0.9% after each dose:
- to avoid re-paralysis (and/or bradycardia with suxamethonium) during recovery period
- because many of these drugs are physically incompatible with other commonly used drugs.

15.02.01 NON-DEPOLARISING NEUROMUSCULAR BLOCKERS
ATRACURIUM
CISATRACURIUM
MIVACURIUM
PANCURONIUM
ROCURONIUM
VECURONIUM

Mode of action
Acetylcholine receptor antagonists which act at the neuromuscular junction preventing depolarisation of the muscle membrane.

Contraindications
Allergy to individual agent
Specific considerations
Myasthenia gravis: prolongs paralysis; avoid neuromuscular blocking agents if possible.
Neuromuscular diseases (eg dystrophia myotonica, history of polio), severe obesity: unpredictable effect; use cautiously and monitor neuromuscular function closely.
Burns: resistance to non-depolarising neuromuscular blockers may develop (increases dosing requirements and shortens duration of action); titrate to response, monitoring neuromuscular function closely. Avoid mivacurium as plasma cholinesterase activity can also be reduced in these patients, prolonging its effect.
Asthma, significant cardiovascular disease: histamine release particularly hazardous; avoid atracurium and mivacurium.
Children: Neonates are generally more sensitive to non-depolarising neuromuscular blocking agents; duration of action may be prolonged; monitor neuromuscular function closely.
In older children, the duration of action is shorter and spontaneous recovery is faster than in adults; maintenance doses are required more frequently; monitor neuromuscular function during use.

Adverse effects
Rare: anaphylactic/anaphylactoid reactions

Comparative information
See Table 15.02 Comparison of non-depolarising neuromuscular blockers

Practice points
- prior administration of suxamethonium shortens onset and may increase depth of neuromuscular blockade produced by non-depolarising agents; reduce dose of non-depolarising drugs and give only after recovery from suxamethonium-induced neuromuscular blockade
- if administered during inhalational anaesthesia, reduce initial dose by 25–33% and maintenance dose by up to 40%
- large doses of non-depolarising agents have shorter onset times but longer recovery times
- repeated administration of maintenance doses have no cumulative effect on the duration of neuromuscular blockade if recovery is allowed to begin before next dose; in this way, repeat doses can be given relatively regularly with predictable results
- myopathy has been reported following prolonged use (>48 hours) in the intensive care unit; monitor neuromuscular function closely

Reversal of neuromuscular blockade
- can be achieved when recovery of muscle twitch in response to peripheral nerve stimulation has started; with most agents (except pancuronium), complete reversal is usually achieved within 8–10 minutes of administration of neostigmine
- give an anticholinergic, eg atropine or glycopyrrolate, with neostigmine to prevent its muscarinic effects (especially bradycardia)
**ATRACURIUM**

**Mode of action**
Acetylcholine antagonists which combine with postjunctional acetylcholine receptors at the neuromuscular junction and prevent depolarisation of the muscle membrane. Anticholinesterase inhibitors, such as neostigmine, can be used to reverse the neuromuscular blockade.

**Indications**
Skeletal muscle relaxation in anaesthesia.

**Contraindications**
Allergy to atracurium, cisatracurium or benzenesulfonic acid.

**Specific considerations**
Asthma, significant cardiovascular disease: histamine release particularly hazardous; use alternative agent.

**Pregnancy**
There have been no demonstrated adverse effects in the fetus or the newborn infant; ADEC category C.

**Lactation**
No data.

**Adverse effects**
Most are suggestive of histamine release which is more common with larger doses and rapid rate of injection.

**Common**:
- hypotension, skin flushing, tachycardia.

**Infrequent**:
- bronchospasm, bradycardia.

**Rare**:
- anaphylactic/anaphylactoid reactions.

**Dosage**

*Adult, child >2 years*
- IV bolus, intubation dose 0.4–0.5 mg/kg, maintenance dose 0.08–0.1 mg/kg. Give over 60 seconds in debilitated or hypovolaemic patients.
- Maintenance IV infusion, 9–10 micrograms/kg/minute after early evidence of spontaneous recovery from the bolus dose, then 5–9 micrograms/kg/minute; adjust according to response.
- Child 1–24 months
  - IV, 0.3–0.6 mg/kg bolus dose for intubation; maintenance dose 0.1–0.2 mg/kg or infusion of 0.3–0.6 mg/kg/hour.

**Practice points**
- not recommended for continuous use over a period of days

**Products**
- ATRACURIUM AMPS/VIAL 25 MG/AMP/VIAL (AS BESYLATE)  2.5 ML AMP OR VIAL (ATACURE®, TRACRIUM®, ACURMIL®)
- ATRACURIUM AMPS/VIAL 50 MG/AMP/VIAL (AS BESYLATE)  5 ML AMP OR VIAL (ATACURE®, ATRACURIUM®, TRACRIUM®, TRACURIX®)

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**CISATRACURIUM**

See under Atracurium

**Specific considerations**
Myasthenia gravis: prolonged paralysis; avoid neuromuscular blocking agents if possible.

Myopathies (eg dystrophy myotonica), severe obesity, after polio: unpredictable effect in magnitude and direction; use cautiously and monitor neuromuscular function closely.

Burns: resistance to non-depolarising neuromuscular blockers may develop resulting in increased dosing requirements and shorter duration of action; titrate to response, monitoring neuromuscular function closely. Avoid mivacurium as plasma cholinesterase activity can also be reduced in these patients, prolonging its effect.

Asthma, significant cardiovascular disease: histamine release particularly hazardous; avoid atracurium and mivacurium.

History of anaphylactoid reaction to neuromuscular blocking agents: allergic cross-reactivity has been reported; refer to specialist for skin testing for sensitivity to other neuromuscular blockers.

Children: Neonates show increased sensitivity to non-depolarising neuromuscular blocking agents in general; duration of action may be prolonged; monitor neuromuscular function closely.

In older children, the duration of action is shorter and spontaneous recovery is faster than in adults; maintenance doses are required more frequently; monitor neuromuscular function during use.

**Pregnancy**
No data; ADEC category C.

**Lactation**
No data.

**Adverse effects**
Infrequent: bradycardia, hypotension, flushing, bronchospasm, rash.

Rare: anaphylactoid/anaphylactic reactions.
Dosage
IV bolus
Adult, 0.15 mg/kg for intubation, then 0.03 mg/kg if required for maintenance.
Child >2 years, 0.1 mg/kg for intubation, then 0.02 mg/kg if required for maintenance.

Maintenance IV infusion
3 micrograms/kg/minute after early evidence of spontaneous recovery from the bolus dose, then 1–2 micrograms/kg/minute; adjust according to response.

Practice points
- the recovery profile after infusion is independent of the duration of infusion and occurs at a rate comparable to that following a single bolus injection.

Products
CISATRACRIUM AMPS 5 MG/AMP (AS BESYLATE) 2.5 ML AMP (NIMBEX®)

MIVACURIUM
See under Atracurium

Specific considerations
Asthma, significant cardiovascular disease: histamine release particularly hazardous; avoid use.
Low or atypical plasma cholinesterase: prolonged paralysis may occur; use alternative agent if possible.
Renal impairment: Duration of neuromuscular block is 1.5 times longer in endstage renal failure; adjust dose according to response.
Hepatic impairment: Reduced plasma cholinesterase activity in endstage hepatic failure; duration of neuromuscular block is 3 times longer; adjust dose according to response.
Elderly: Onset time, duration of action and recovery rate 20–30% longer than in younger patients; monitor neuromuscular function during use.
Pregnancy: No data; ADEC category B2.
Lactation: No data.

Adverse effects
Most have been attributed to histamine release which is more common when larger doses (>0.2 mg/kg) are used and injected rapidly.
Common: flushing.
Infrequent: hypotension, tachycardia, bradycardia, cardiac arrhythmia, phlebitis, bronchospasm, rash, injection site reaction.
Rare: anaphylactoid/anaphylactic reactions.

Dosage
Adult
IV bolus
Intubation, 0.07–0.25 mg/kg over 30–60 seconds.
Maintenance, 0.1 mg/kg.
Significant cardiovascular disease, severe renal or hepatic impairment, maximum dose 0.15 mg/kg.

Maintenance IV infusion
8–10 micrograms/kg/minute after early evidence of spontaneous recovery from the bolus dose, adjust according to response in increments of 1 microgram/kg/minute no less than every 3 minutes; usual maintenance dose 6–7 micrograms/kg/minute.
Child >2 months
IV bolus, 0.1–0.2 mg/kg for intubation, maintenance dose 0.1 mg/kg.
IV infusion, usual maintenance, 10–15 micrograms/kg/minute.

Practice points
- although mivacurium is hydrolysed by plasma cholinesterase, the anticholinesterases used in anaesthetic practice have been shown to reverse rather than prolong its effects
- once spontaneous recovery has started, it is complete in approximately 15 minutes and is independent of the dose administered; reversal with an anticholinesterase may not be routinely required because it shortens recovery time by only 5–6 minutes
- spontaneous recovery of neuromuscular function after infusion for up to 2.5 hours is independent of the duration of infusion and is comparable to that following a single dose; limited data are available for infusions longer than this
PANCURONIUM
See under Atracurium
Contraindications
Allergy to pancuronium.
Specific considerations
Pre-existing tachycardia, hypertension (including that associated with renal failure or phaeochromocytoma): avoid use, alternative agents available.
Renal impairment: Prolonged neuromuscular blockade may occur; reduction of maintenance doses may be necessary. Avoid in severe renal impairment.
Hepatic impairment: Increased onset time and prolonged neuromuscular blockade and recovery time may occur; monitor neuromuscular blockade closely.
Pregnancy: Safe to use; ADEC category B2.
Lactation: No data.
Adverse effects
Common: hypertension, tachycardia.
Rare: anaphylactic/anaphylactoid reactions.
Dosage
Adult, child >1 month: IV bolus, 0.05–0.1 mg/kg for intubation, maintenance dose 0.01–0.02 mg/kg.
Neonate: IV bolus, 0.1–0.15 mg/kg for intubation, maintenance dose 0.1 mg/kg.
Practice points
• prior administration of suxamethonium shortens the onset and may increase the depth of neuromuscular blockade produced by non-depolarising agents; reduce dose of non-depolarising drugs and give only after recovery from suxamethonium-induced neuromuscular blockade
• reduce initial dose by 25–33% and maintenance dose by up to 40% if administered during inhalational anaesthesia
• large doses of non-depolarising agents have shorter onset times but longer recovery times
• repeated administration of maintenance doses have no cumulative effect on the duration of neuromuscular blockade if recovery is allowed to begin before repeat dosing; in this way, repeat doses can be given at relatively regular intervals with predictable results
• reversal of neuromuscular blockade can be achieved when recovery of muscle twitch in response to peripheral nerve stimulation has started; with most agents (except pancuronium), complete reversal is usually achieved within 8–10 minutes of administration of anticholinesterase inhibitors
• myopathy has been reported following prolonged use (>48 hours) in the intensive care unit; monitor neuromuscular function closely
• give an anticholinergic agent, such as atropine or glycopyrrolate, with the anticholinesterase inhibitors to prevent the muscarinic effects (especially bradycardia) of these reversal agents

Products
PANCURONIUM AMPS 4 MG/AMP (AS BROMIDE) 2 ML AMP (ALPAX®, PANCURONIUM RICHMOND®, PAVULON®)

ROCURONIUM
Mode of action
Acetylcholine receptor antagonist which acts at the neuromuscular junction preventing depolarisation of the muscle membrane.
Indications
Skeletal muscle relaxation in anaesthesia and intensive care.
Contraindications
Allergy to individual agent.
Specific considerations
Renal impairment: Duration of action may be prolonged in renal impairment; reduction in infusion rate may be required; monitor neuromuscular function and titrate to effect.
Hepatic impairment: Duration of action may be prolonged in hepatic or biliary diseases; reduction in infusion rate may be required; monitor neuromuscular function and titrate to effect.

**Adverse effects**

The incidence increases with increasing dosage. Common: rash, pain on injection (particularly during rapid sequence induction). Infrequent: tachycardia (especially with doses >0.9 mg/kg), bronchospasm, urticaria. Rare: anaphylactic/anaphylactoid reactions.

**Dosage**

Adult, child >1 month

**IV bolus**

Intubation, 0.6 mg/kg; 1 mg/kg for rapid sequence induction (see **Practice points**).

Maintenance, 0.15 mg/kg.

**Maintenance IV infusion**

5–10 micrograms/kg/minute (0.3–0.6 mg/kg/hour) after early evidence of spontaneous recovery from the bolus dose; adjust according to response.

Elderly, significant renal or hepatic disease

**IV bolus**

Intubation, 0.6 mg/kg.

Maintenance, 0.075–0.1 mg/kg.

**Maintenance IV infusion**

5–6 micrograms/kg/minute (0.3–0.4 mg/kg/hour); adjust according to response.

**Practice points**

- main advantage is faster development of neuromuscular block
- useful alternative to suxamethonium for rapid sequence induction, but its duration of action is much longer
- spontaneous recovery following infusion is similar to that after single bolus dose

**Products**

ROCURONIUM VIALS 10 MG/ML 5 ML VIAL (ESMERON®)

**VECURONIUM**

**Mode of action**

Acetylcholine antagonist which combines with postjunctional acetylcholine receptors at the neuromuscular junction and prevent depolarisation of the muscle membrane. Anticholinesterase inhibitors, such as neostigmine, can be used to reverse the neuromuscular blockade.

**Indications**

Skeletal muscle relaxation in anaesthesia.

**Contraindications**

Allergy to vecuronium

**Specific considerations**

Renal impairment: Duration of action may be prolonged; use cautiously.

Hepatic impairment: Decreased clearance resulting in prolonged duration of action; use alternative agents.

Pregnancy: ADEC category C.

Lactation: No data.

**Adverse effects**

Rare: anaphylactic/anaphylactoid reactions.

**Dosage**

**Adult**

**IV bolus**, 0.1 mg/kg for intubation, maintenance 0.02–0.04 mg/kg.

**IV infusion**, 1 microgram/kg/minute (0.06 mg/kg/hour), adjust according to response.

**Child**

**IV bolus**, 0.1 mg/kg for intubation, repeated as required for maintenance.

**Practice points**

- prior administration of suxamethonium shortens the onset and may increase the depth of neuromuscular blockade produced by non-depolarising agents; reduce dose of non-depolarising drugs and give only after recovery from suxamethonium-induced neuromuscular blockade.
• reduce initial dose by 25–33% and maintenance dose by up to 40% if administered during inhalational anaesthesia
• large doses of non-depolarising agents have shorter onset times but longer recovery times
• repeated administration of maintenance doses have no cumulative effect on the duration of neuromuscular blockade if recovery is allowed to begin before repeat dosing; in this way, repeat doses can be given at relatively regular intervals with predictable results
• reversal of neuromuscular blockade can be achieved when recovery of muscle twitch in response to peripheral nerve stimulation has started; with most agents (except pancuronium), complete reversal is usually achieved within 8–10 minutes of administration of anticholinesterase inhibitors
• myopathy has been reported following prolonged use (>48 hours) in the intensive care unit; monitor neuromuscular function closely
• give an anticholinergic agent, such as atropine or glycopyrrolate, with the anticholinesterase inhibitors to prevent the muscarinic effects (especially bradycardia) of these reversal agents.

Products
VECURONIUM AMPS 4 MG/AMP (AS BROMIDE) 1 ML AMP (NORCURON®)

15.02.02 DEPOLARISING NEUROMUSCULAR BLOCKERS

SUXAMETHONIUM
Also known as succinylcholine.

Mode of action
Suxamethonium mimics acetylcholine by combining with the acetylcholine receptor, causing depolarisation of the motor end plate and resulting in neuromuscular blockade.

Indications
Skeletal muscle relaxation in anaesthesia (rapid onset, short acting).

Contraindications
Allergy to suxamethonium.
Personal or family history of malignant hyperthermia.
Muscular dystrophies, congenital myopathies.
After the acute phase of injury following major burns or multiple trauma.
Neurological disease involving extensive muscle wasting.

Specific considerations
Penetrating eye injury, acute narrow angle glaucoma: may increase intraocular pressure; use cautiously.
Potential causes of hyperkalaemia: increased risk of hyperkalaemia; avoid use, particularly if pre-existing hyperkalaemia.
Low or abnormal plasma cholinesterase, family history of suxamethonium apnea: prolonged paralysis may occur; use alternative agent if possible.
Myasthenia gravis: unpredictable response to suxamethonium, but can develop dual block; avoid if possible.
Phaeochromocytoma: muscle fasciculations may provoke catecholamine release; use alternative agent if possible.
Renal impairment: Serum potassium concentration increases to the same extent as in normal individuals; if the patient has hyperkalaemia before administration of suxamethonium, avoid use as there is a risk of arrhythmias and cardiac arrest.
Pregnancy: Safe to use; ADEC category A.
Lactation: No data; use with caution.

Adverse effects
Common: muscle fasciculations, postoperative muscle pains, bradycardia (particularly with repeated dosing), excessive salivation, increased intraocular, intracranial and intragastric pressures
Infrequent: tachycardia, arrhythmias, hypertension, hypotension, bronchospasm, jaw rigidity, prolonged neuromuscular blockade, hyperkalaemia
Rare: malignant hyperthermia, anaphylactoid/anaphylactic reactions, myoglobinemia, myoglobinuria, rhabdomyolysis
Dual (phase II) block
Occurs after high or repeated doses of suxamethonium; the initial depolarising block changes to a non-depolarising block which can be prolonged. Continue mechanical ventilation and anaesthesia for as long as required. Once a diagnosis of non-depolarising blockade has been made, consider reversal with neostigmine and atropine.
Altered response (low plasma cholinesterase activity)
The activity of this enzyme may be influenced by genetic and acquired factors, leading to an altered response to suxamethonium.
Inherited plasma cholinesterase deficiency:
homozygotes (<0.05% of the population) remain apnoeic for 1–2 hours after receiving suxamethonium and develop a dual (phase II) block during this time.
heterozygotes (3.8% of the population) have little or no disturbance and remain apnoeic for approximately 10 minutes.
Acquired plasma cholinesterase deficiency may occur with conditions such as pregnancy, severe liver disease, cardiac or renal failure, burns, severe anaemia, cancer, malnutrition, hypothyroidism, collagen diseases and in patients undergoing plasmapheresis. In addition, the activity of plasma cholinesterase can be reduced by drugs and organophosphate pesticides. The normal half-life of plasma cholinesterase is 2 weeks.
Management is based on mechanical ventilation and maintenance of anaesthesia until recovery occurs. Afterwards the patient and the family should be investigated to determine the nature and extent of the abnormality.
Malignant hyperthermia (MH)
A rare, inherited, hypermetabolic response of skeletal muscle which can be triggered by certain drugs, especially suxamethonium and inhalational agents. It may occur abruptly and unpredictably and can be fatal. It results in increased oxygen consumption and carbon dioxide production, tachypnoea, tachycardia, arrhythmias, muscle rigidity, rising temperature and metabolic acidosis. Treatment includes stopping the anaesthetic if possible (if not possible, switch to MH-safe agents), giving oxygen, IV dantrolene, fluid and electrolytes and lowering temperature.

Dosage
Adult
IV bolus, 0.5–1.2 mg/kg over 10–30 seconds for intubation; incremental doses of 0.25–0.6 mg every 5–7 minutes as required for maintenance; maximum 500 mg/hour.
IV infusion (diluted to 1–2 mg/mL), 2.5–4 mg/minute; maximum 500 mg/hour.
IM, up to 2.5 mg/kg, maximum dose 150 mg.
Child
Neonate and infant, IV bolus 2 mg/kg for intubation.
Child, IV bolus 1 mg/kg for intubation.
IM, 2.5–4 mg/kg, maximum dose 150 mg.

Patient counselling
You may have muscle pains for about 24 hours after your operation, particularly around your neck, shoulders and chest.

Practice points
- after IV administration, the onset of action occurs between 30–60 seconds and lasts for 3–5 minutes; after IM injection, onset usually occurs in 3 minutes and lasts 10–30 minutes; larger doses produce more prolonged muscle relaxation
- give suxamethonium after induction of anaesthesia because paralysis is usually preceded by painful muscle fasciculations; these can be attenuated by prior administration of a small dose of non-depolarising agent, but the neuromuscular blocking action of suxamethonium may be decreased; increase dose of suxamethonium by 30–50%
- profound bradycardia (and asystole) is more common after a second dose of suxamethonium, particularly in children; unless contraindicated, pretreat all patients with atropine to reduce risk
- serum potassium concentration is briefly increased in normal individuals by 0.2–0.5 mmol/L
- IM administration is rarely indicated
- continuous IV infusions are not recommended because of risk of dual (phase II) block; alternative agents are available.

Products
SUXAMETHONIUM AMPS 100 MG/AMP (AS CHLORIDE) 2 ML AMP (MIDARINE®)

15.04 DRUGS FOR LOCAL ANAESTHESIA

LOCAL ANAESTHESIA
In general, smaller nerve fibres are more sensitive to the action of local anaesthetics than large fibres. Therefore, loss of pain and temperature sensation is the first sign of neural blockade, followed by loss of proprioception and touch, and finally loss of motor activity, which requires the highest concentrations of local anaesthetic. Increased skin
temperature may occur early when sympathetic nerves are blocked.

**Clinical uses**
Topical anaesthesia: used before venipuncture or split skin grafting; to facilitate instrumentation (eg cystoscopy); for procedures involving the eye surface and in dental practice.
SC infiltration: for localised anaesthesia where motor nerve block is not required.
Intra-articular/intra-tendonous injection—for relief of pain caused by inflammation (local anaesthetic with corticosteroid).
Ophthalmic anaesthesia: used for peribulbar, retrobulbar and sub-Tenon's block to facilitate eye surgery.
Hyaluronidase is often combined with the local anaesthetic to improve the quality of the block and increase its speed of onset; however, there is an increased risk of systemic toxicity.
Peripheral nerve or nerve plexus block: for surgery within a specific nerve or plexus distribution (local anaesthetic alone, or with sedation or general anaesthesia), and for postoperative pain relief.
Central neural blockade (epidural/caudal/intrathecal): for major surgery (local anaesthetic alone, or with opioids, with or without sedation or general anaesthesia); for acute postoperative pain relief and during labour and delivery (local anaesthetic alone or with opioids); chronic pain relief (local anaesthetic with corticosteroid); and for cancer and neuropathic pain (local anaesthetic with drugs such as opioids, midazolam, clonidine).
IV regional anaesthesia (IVRA): used for peripheral limb surgery (Bier's block) and for sympathetic limb blockade.
Sympathetic plexus block—for symptom relief in selected chronic pain states, peripheral vascular disease and Raynaud's disease.

**Complications**
Local anaesthetics are generally safe if used as recommended. Most adverse effects relate to technique (eg resulting in systemic toxicity) or to the effects of the block (eg hypotension during epidural or intrathecal anaesthesia), rather than to the drugs.
Toxicity due to local anaesthetic
High plasma concentrations may result from accidental intravascular injection, rapid absorption or rate of administration, excessive dosage or delayed elimination. Systemic toxicity affects the CNS and cardiovascular systems in particular. In general, lower drug concentrations produce CNS symptoms and signs, which usually occur first, followed by cardiovascular effects at higher concentrations. Occasionally, cardiovascular collapse may precede CNS toxicity with little warning (particularly with bupivacaine).
Central nervous system
Usually excitation (nervousness, circumoral tingling, tinnitus, tremor, dizziness, blurred vision, seizures), followed by depression (drowsiness, loss of consciousness, respiratory depression and apnea). The excitatory effects may be very brief or even absent, and CNS depression may present first.
Management: maintain airway and give oxygen; ventilate and add anticonvulsants (eg diazepam, clonazepam, thiopentone) if necessary.
Cardiovascular system
Hypotension, bradycardia, arrhythmias, cardiac arrest. Often due to hypoxaemia secondary to respiratory depression, but may result from direct myocardial depression and vasodilatation.
Management: elevate legs; give oxygen, IV fluids, vaspressors (eg ephedrine), and/or inotropes; add atropine if marked bradycardia. Treat cardiac and/or respiratory arrest according to standard protocols; prolonged resuscitation may be required.

**Neurological complications of procedure**
Postdural puncture headache following accidental subarachnoid puncture during epidural block is the commonest neurological complication of central neural blockade.
Inadvertent subarachnoid injection can lead to cardiovascular collapse, CNS depression and respiratory arrest.
Other neurological complications include paraesthesia, persistent anaesthesia, weakness or paralysis, loss of sphincter control, anterior spinal artery occlusion, cauda equina syndrome and arachnoiditis.
Pressure sores and nerve palsies may occur with dense blocks; compartment syndrome may be masked in anaesthetic limbs.

**Prevention of complications**
Personnel: local anaesthetics and techniques should be used only by doctors with appropriate training; airway management and resuscitation equipment must be readily available.
Careful monitoring of respiratory, cardiovascular and neurological function, including level of consciousness, is necessary for at least the first 45 minutes after injection; monitoring for a longer period of time may be required for procedures associated with delayed absorption. Maintain verbal contact during administration and procedure.
Optimise the patient's condition before a major block. Establish large bore IV access for fluid administration before performing epidural or intrathecal anaesthesia to manage hypotension and bradycardia.
Concentration of drug: high concentrations of local anaesthetic are relatively more toxic dose for dose than weaker ones; use the lowest dose at the weakest concentration that produces desired effect.
Cumulative dose: to avoid toxicity, add up total dose and consider half-lives elapsed before giving supplemental doses. When prolonged analgesia is required, consider a long acting local anaesthetic.
Rate of systemic absorption: is related to vascularity of injection site (intercostal > epidural > brachial plexus > SC). Absorption through mucous membranes may also be rapid and care is essential to avoid toxicity. Avoid applying local anaesthetics to the skin for prolonged periods or over extensive areas.
Administration: inject local anaesthetics slowly and incrementally (3–5 mL at a time) and aspirate gently and frequently to avoid intravascular injection. Since negative aspiration does not preclude this, allow a sufficient pause between each bolus to identify systemic effects.
Combination with other drugs: such as opioids or clonidine can potentiate analgesia allowing a lower concentration of local anaesthetic to be used, reducing motor block and the risk of adverse effects.

Central neural blockade in anticoagulated patients
These patients are at risk of developing an epidural or intrathecal haematoma which can cause paralysis. Risk is increased by the use of indwelling epidural catheters, traumatic or repeated epidural/intrathecal puncture, and drugs affecting clotting such as NSAIDs, platelet inhibitors or other anticoagulants.
Therapeutic anticoagulation: consult local protocols.
Prophylactic anticoagulation: if possible, perform block or remove catheter at least 12 hours after last dose and 2 hours before the next dose of anticoagulant. Monitor closely for signs and symptoms of neurological deficit.

Practice points
- resuscitation equipment and drugs, including oxygen, should be immediately available; insert an IV cannula before performing local anaesthetic techniques
- the onset and duration of anaesthesia depend on the route of administration, status of the patient, the dosage (volume and concentration) and the use of vasoconstrictors
- duration of anaesthesia is determined by the total dose rather than either the volume or concentration used; however, for epidural anaesthesia, the quality and extent of the blockade is determined by the volume as well as the total dose of the drug
- increasing motor block is more likely with increasing concentration of local anaesthetic; after central neural blockade, dense motor block may mask development of epidural haematoma or abscess
- urinary retention may also occur after central neural blockade
- small doses of local anaesthetics injected into the head and neck area may result in accidental intravascular or subarachnoid injection; this may produce adverse reactions similar to those seen with inadvertent intravascular injection of larger doses
- fetal bradycardia frequently follows paracervical block and may be associated with fetal acidosis and hypoxia
- depending on dosage, local anaesthesia may have a mild effect on mental function and may temporarily impair motor ability and coordination.

BUPIVACAINE
Mode of action
Reversibly interrupts impulse conduction in peripheral nerves and stabilizes excitable cell membranes by blocking sodium channels, thus inhibiting depolarisation.

Indications
Marketed: Infiltration, nerve block, epidural and intrathecal anaesthesia.
Accepted: Ophthalmic procedures.

Contraindications
Do not use for IV regional anaesthesia (IVRA).
Previous allergic reaction to local anaesthetic of the same group (ie ester or amide).
Local inflammation or infection.

For contraindications for central neural blockade.

Specific considerations
Hyperthyroidism: increases risk of toxicity; use cautiously.

Pregnancy: Safe to use; the lowest effective concentration should always be used, eg 0.125% for epidural analgesia in labour, 0.5% for caesarean section. ADEC category A (combinations with fentanyl, ADEC category C).
Hepatic impairment: Severe impairment and reduced hepatic blood flow (eg heart failure) decrease clearance of lignocaine and procaine; also increased risk of toxicity with prolonged or repeated administration of other local.
detectable.

Elderly: Increased sensitivity; reduce dose.

Children: Children <6 months are more sensitive to toxic effects; reduce dose.

Pregnancy: Most are ADEC category A.

Local anaesthetic requirements for central blockade are reduced in pregnancy, due to increased sensitivity and alterations in anatomy of epidural space.

Lactation: Unlikely to cause problems.

**Adverse effects**

Markedly cardiotoxic; cardiac arrest secondary to bupivacaine toxicity is extremely difficult to reverse and may require prolonged resuscitation.

If administered correctly, those resulting from the drugs themselves are rare and include allergic reactions; adverse effects from added vasoconstrictors also occur.

Allergy: Allergy to all local anaesthetics is rare, but is relatively more common with esters than amides. There is no cross-reactivity between the 2 groups. It may present as localised edema, urticaria, bronchospasm and anaphylaxis. Rash may occur following skin application.

Preservatives in the products (eg methylparaben, sodium metabisulfitfe) can also cause allergic reactions.

Vasoconstrictor reaction: This can manifest as anxiety, pallor, tachycardia, hypertension, sweating or arrhythmias. It usually resolves on stopping administration.

**Dosage**

Maximum

- Adult, 2 mg/kg as a single dose; 400 mg in 24 hours.
- Child, 2 mg/kg as a single dose or 0.125–0.3 mg/kg/hour of 0.125%. Limit infusion time to 36 hours for neonates and 48 hours for small infants.
- Infiltration: 12.5–150 mg of 0.25% (5–60 mL) or 0.5% (2.5–30 mL).
- Nerve block: Bolus, 12.5–150 mg of 0.25% (5-60 mL) or 0.5% (2.5-30 mL).
- Infusion, 10–12.5 mg/hour of 0.125% (8–10 mL/hour) or 0.25% (4–5 mL/hour).
- Ophthalmic: Peribulbar, up to 50 mg (10 mL) of 0.5%. Retrobulbar, 15–20 mg (3–4 mL) of 0.5%.
- Combination treatment: 0.5% bupivacaine is often combined with hyaluronidase (10–50 units/mL) and/or lignocaine 2% for ophthalmic procedures.
- Epidural for surgery (including caesarean section): 75–150 mg (15–30 mL) of 0.5%.
- Epidural for analgesia: 25–50 mg (10–20 mL) of 0.25%; administer at intervals of at least 15 minutes up to a maximum of 150 mg over 4 hours.
- Combination treatment: 7.5–12.5 mg (6–10 mL) of bupivacaine 0.125% with fentanyl 5 micrograms/mL.
- Epidural infusion: 6.25–18.75 mg/hour of 0.125% (5–15 mL/hour) or 0.25% (2.5–7.5 mL/hour).
- Combination treatment: 3.75–12.5 mg/hour (3–10 mL/hour) of bupivacaine 0.125% with fentanyl 5 micrograms/mL.
- Intrathecal: 15–20 mg (3–4 mL) of 0.5%. 5–20 mg (1–4 mL) of 0.5% heavy (with glucose 80 mg/mL).

Concentrations of local anaesthetics are expressed as a percentage or in mg/mL. Multiply by 10 to convert from percentage to mg/mL (eg 0.5% = 5 mg/mL).

Maximum doses are given for most local anaesthetics, but consider them only as a guide because blood concentrations depend on many factors, including the area to be anaesthetised, the vascularity of the tissues, the technique used and the tolerance and physical condition of the individual. The dose administered is also influenced by the intensity of the block, the degree of muscle relaxation and the duration of anaesthesia or analgesia required. The dose for epidural anaesthesia is determined by the number of segments to be blocked, and is usually 2–3 mL/segment. For epidural analgesia, the required dose depends on the correct positioning of the epidural catheter adjacent to the relevant nerve roots.

With ophthalmic blocks, the volume of local anaesthetic used depends on the intraorbital compliance on injection in addition to the volume required to achieve ocular akinesia and analgesia.

**Use of vasoconstrictors**

Most local anaesthetics (except cocaine) cause vasodilation. The duration of action of some agents can be extended by adding adrenaline, which causes vasoconstriction reducing local blood flow, slowing the rate of absorption of the local anaesthetic and prolonging its local effect.

The maximum total dose of adrenaline is 500 micrograms; concentrations >5 micrograms/mL (1:200 000) produce little additional benefit and are not usually advised.

Vasoconstrictors are contraindicated in IVRA, with ergot oxytocics or near terminal arteries (fingers, toes, ears, penis) and are not recommended in intrathecal anaesthesia. Use with caution in patients with heart disease and/or hypertension, hyperthyroidism and in the presence of halogenated inhalational agents (increased risk of arrhythmias). Felypressin, a non-catecholamine vasoconstrictor, is used as an alternative to adrenaline in dental preparations.
Patient counselling
Advise patient about onset and duration of action, other subjective sensations specific to the particular block and behaviour modification to avoid injury to anaesthetised area.

Practice points
- recommended doses should not be repeated more frequently than every 3 hours; specialists may use higher doses; for alternative regimens and combinations, consult local protocols
- highly lipid-soluble; adding adrenaline prolongs block less than with other local anaesthetics
- long duration of action (generally 3–14 hours); postoperative analgesia can last 3–4 hours after epidural blockade and 7–14 hours after intercostal blockade; residual effects may be present for 24–48 hours
- bupivacaine 0.25% produces incomplete motor block and can be used when muscle relaxation is not important; 0.5% produces a greater degree of motor block when used for epidural or nerve block, and this increases with repeat doses

Products
BUPIVACAINE VIAL 0.5 % (AS HCL) 4 ML VIAL (MARCAINE SPINAL HEAVY®)
BUPIVACAINE VIAL 0.5 % (AS HCL) 20 ML VIAL (BUCAINE®, MARCAINE SPINAL HEAVY®)

COCOIlw
Mode of action
Reversibly interrupts impulse conduction in peripheral nerves and stabilizes excitable cell membranes by blocking sodium channels, thus inhibiting depolarisation.

Indications
Topical anaesthesia for fibre-optic endotracheal intubation.
Topical anaesthesia in ENT procedures.

Contraindications
Administration by injection.
Treatment with, or within 14 days of stopping, a MAOI.
Previous allergic reaction to local anaesthetic of the same group (ie ester or amide).
Local inflammation or infection.

Specific considerations
Cardiac disease, hypertension, hyperthyroidism: increase risk of cardiotoxicity; use cautiously.
Damaged mucosa: risk of systemic toxicity from enhanced absorption; avoid use.
Treatment with sympathomimetics: increases risk of cardiac arrhythmias.

Adverse effects
Cocaine is rapidly absorbed from the nasal mucosa; when administered on gauze ribbons or plugs it is easy to exceed the recommended dose. Common signs of toxicity are headache, nausea, vomiting and abdominal pain. Excitement, hallucinations, restlessness, confusion associated with tachycardia, hypertension, tachypnoea and an increase in body temperature can occur. Ventricular fibrillation, seizures, coma and death may follow.
Cardiovascular toxicity due to cocaine may be related to individual sensitivity and therefore may not be predictable or dose-dependent. Severe toxic effects have occurred with doses as low as 20 mg.
If administered correctly, those resulting from the drugs themselves are rare and include allergic reactions; adverse effects from added vasoconstrictors also occur.
Allergy: Allergy to all local anaesthetics is rare, but is relatively more common with esters than amides. There is no cross-reactivity between the 2 groups. It may present as localised edema, urticaria, bronchospasm and anaphylaxis. Rash may occur following skin application.
Preservatives in the products (eg methylparaben, sodium metabisulfite) can also cause allergic reactions.
Vasoconstrictor reaction: This can manifest as anxiety, pallor, tachycardia, hypertension, sweating or arrhythmias. It usually resolves on stopping administration.

Dosage
Solutions of 1–10% are used topically; administer the lowest dose necessary. Maximum dose 1.5 mg/kg as a single dose. Toxic dose, 3 mg/kg.
Concentrations of local anaesthetics are expressed as a percentage or in mg/mL. Multiply by 10 to convert from percentage to mg/mL (eg 0.5% = 5 mg/mL).
Maximum doses are given for most local anaesthetics, but consider them only as a guide because blood concentrations depend on many factors, including the area to be anaesthetised, the vascularity of the tissues, the technique used and the tolerance and physical condition of the individual. The dose administered is also influenced by the intensity of the block, the degree of muscle relaxation and the duration of anaesthesia or analgesia required.
The dose for epidural anaesthesia is determined by the number of segments to be blocked, and is usually 2–3 mL/segment. For epidural analgesia, the required dose depends on the correct positioning of the epidural catheter adjacent to the relevant nerve roots.

With ophthalmic blocks, the volume of local anaesthetic used depends on the intraorbital compliance on injection in addition to the volume required to achieve ocular akinesia and analgesia.

**Use of vasoconstrictors**

Most local anaesthetics (except cocaine) cause vasodilation. The duration of action of some agents can be extended by adding adrenaline, which causes vasoconstriction reducing local blood flow, slowing the rate of absorption of the local anaesthetic and prolonging its local effect.

The maximum total dose of adrenaline is 500 micrograms; concentrations >5 micrograms/mL (1:200 000) produce little additional benefit and are not usually advised.

Vasoconstrictors are contraindicated in IVRA, with ergot oxytocics or near terminal arteries (fingers, toes, ears, penis) and are not recommended in intrathecal anaesthesia. Use with caution in patients with heart disease and/or hypertension, hyperthyroidism and in the presence of halogenated inhalational agents (increased risk of arrhythmias). Felypressin, a non-catecholamine vasoconstrictor, is used as an alternative to adrenaline in dental preparations.

**Patient counselling**

Advise patient about onset and duration of action, other subjective sensations specific to the particular block and behaviour modification to avoid injury to anaesthetised area.

**Practice points**

- after applying to mucous membranes, onset of action occurs within 1 minute, is maximal within about 5 minutes and may last for 20–30 minutes, depending on dose and concentration used
- in addition to blocking nerve impulse conduction, cocaine is also a potent indirect-acting sympathomimetic agent; many of the signs of toxicity of cocaine are the result of sympathetic overactivity
- cocaine with adrenaline is sometimes used in ENT surgery to improve the operative field and reduce absorption, although adrenaline may not add significantly to vasoconstriction and may cause cardiac arrhythmias

**Products**

**COCAIN SOLUTION 4 % BP, USP (NOT REGISTERED)**

**LIDOCAINE (LIGNOCAINE) (LOCAL)**

**Mode of action**

Reversibly interrupts impulse conduction in peripheral nerves and stabilizes excitable cell membranes by blocking sodium channels, thus inhibiting depolarisation.

**Indications**

Topical, infiltration, nerve block, ophthalmic, epidural and intrathecal anaesthesia, and IV regional anaesthesia (IVRA)

**Contraindications**

Previous allergic reaction to local anaesthetic of the same group (ie ester or amide)
Local inflammation or infection
For contraindications for central neural blockade.

**Specific considerations**

Porphyria: may induce acute crisis.
Pregnancy: ADEC category A.
Cardiogenic shock, myocardial ischaemia: risk of increased cardiovascular depressant effects.
Severe bradycardia, heart block, impaired cardiac conduction: enhanced conduction defect.
Acidosis, hypoxia, hyperkalaemia: increased risk of toxicity.
Debilitated patients: more sensitive to adverse and anaesthetic effects; reduce dose and monitor carefully.
Neuromuscular disease (eg myasthenia gravis): increased sensitivity to anaesthetic; may increase muscle weakness and depress respiration with central neural blockade; assess risks and benefits before use.
Pre-existing neurological disease: administration of local anaesthetics may worsen condition; assess risks and benefits before use.
Plasma cholinesterase deficiency: marked reduction of ester local anaesthetic metabolism; use alternative local anaesthetic agent.

Treatment with antiarrhythmics: additive myocardial depressant effects which may be clinically important if significant systemic absorption of local anaesthetic occurs; use cautiously and monitor clinically.
Renal impairment: Toxicity due to accumulation may develop with prolonged or repeated administration; increased...
risk of systemic toxicity with bupivacaine, procaine and ropivacaine in severe renal dysfunction; use with caution. 
Hepatic impairment: Severe impairment and reduced hepatic blood flow (eg heart failure) decrease clearance of 
lignocaine and procaine; also increased risk of toxicity with prolonged or repeated administration of other local 
analgesics.
Elderly: Increased sensitivity; reduce dose.
Children: Children <6 months are more sensitive to toxic effects; reduce dose.
Pregnancy: Most are ADEC category A.
Local anaesthetic requirements for central blockade are reduced in pregnancy, due to increased sensitivity and 
alterations in anatomy of epidural space.
Lactation: Unlikely to cause problems.

Adverse effects
If administered correctly, those resulting from the drugs themselves are rare and include allergic reactions; adverse 
effects from added vasoconstrictors also occur.
Allergy: Allergy to all local anaesthetics is rare, but is relatively more common with esters than amides. There is no 
cross-reactivity between the 2 groups. It may present as localised edema, urticaria, bronchospasm and anaphylaxis.

Rash may occur following skin application.
Preservatives in the products (eg methylparaben, sodium metabisulfite) can also cause al
lergic reactions.
Vasoconstrictor reaction: This can manifest as anxiety, pallor, tachycardia, hypertension, sweating or arrhythmias. It 
usually resolves on stopping administration.

Dosage
Maximum
Adult, 3 mg/kg up to 200 mg as a single dose; for intrathecal anaesthesia, maximum dose 100 mg.
Child, 3 mg/kg as a single dose. Use concentrations of 1% or less for most procedures in children.
Combination with adrenaline: Adult and child, lignocaine 7 mg/kg with adrenaline 5 micrograms/mL (1:200 000).
Topical uses
Pharynx/larynx, 4% topical liquid or 10% spray (1 metered dose = 10 mg).
Upper GIT, 2% viscous oral liquid.
Instrument lubrication, 2% gel or 5% ointment.
Urethra, 2% gel with or without chlorhexidine.
Infiltration: Up to 200 mg of 0.5% (40 mL) or 1% (20 mL).
Combination with adrenaline: Up to 500 mg of lignocaine 0.5% (100 mL) or 1% (50 mL) or 2% (25 mL) with 
adrenaline 5 micrograms/mL (1:200 000).
Nerve block: 30–100 mg of 1% (3–10 mL).
Combination with adrenaline: 30–500 mg of lignocaine 1% (3–50 mL) or 1.5% (2–30 mL) with adrenaline 
5 micrograms/mL (1:200 000).
Ophthalmic: Peribulbar, up to 7.5 mL of 2% (150 mg), with bupivacaine 0.5% (with or without hyaluronidase 10– 
50 units/mL).
Epidural: 100–200 mg of 1% (10–20 mL) or 2% (5–10 mL).
Combination with adrenaline: 150–500 mg of lignocaine 1% (15–50 mL) or 1.5% (10–30 mL) or 2% (7.5–25 mL) 
with adrenaline 5 micrograms/mL (1:200 000).
Intrathecal: 40–80 mg of 2% (2–4 mL).
IVRA: 200 mg of 0.5% (40 mL).

Concentrations of local anaesthetics are expressed as a percentage or in mg/mL. Multiply by 10 to convert from 
percentage to mg/mL (eg 0.5% = 5 mg/mL).
Maximum doses are given for most local anaesthetics, but consider them only as a guide because blood 
concentrations depend on many factors, including the area to be anaesthetised, the vascularity of the tissues, the 
technique used and the tolerance and physical condition of the individual. The dose administered is also influenced 
by the intensity of the block, the degree of muscle relaxation and the duration of anaesthesia or analgesia required.
The dose for epidural anaesthesia is determined by the number of segments to be blocked, and is usually 2– 
3 mL/segment. For epidural analgesia, the required dose depends on the correct positioning of the epidural catheter 
adjacent to the relevant nerve roots.
With ophthalmic blocks, the volume of local anaesthetic used depends on the intraorbital compliance on injection in 
addition to the volume required to achieve ocular akinesia and analgesia.
Use of vasoconstrictors
Most local anaesthetics (except cocaine) cause vasodilation. The duration of action of some agents can be extended 
by adding adrenaline, which causes vasoconstriction reducing local blood flow, slowing the rate of absorption of the 
local anaesthetic and prolonging its local effect.
The maximum total dose of adrenaline is 500 micrograms; concentrations >5 micrograms/mL (1:200 000) produce little additional benefit and are not usually advised.

Vasoconstrictors are contraindicated in IVRA, with ergot oxytocics or near terminal arteries (fingers, toes, ears, penis) and are not recommended in intrathecal anaesthesia. Use with caution in patients with heart disease and/or hypertension, hyperthyroidism and in the presence of halogenated inhalational agents (increased risk of arrhythmias). Felypressin, a non-catecholamine vasoconstrictor, is used as an alternative to adrenaline in dental preparations.

**Patient counselling**
Advise patient about onset and duration of action, other subjective sensations specific to the particular block and behaviour modification to avoid injury to anaesthetized area.

**Practice points**
- onset of action is 1–5 minutes after infiltration and 5–15 minutes after other types of administration; length of action is generally 1–3 hours, but varies with type of block, dose and vasoconstrictor use
- do not repeat the maximum dose at intervals of <1.5 hours
- apply EMLA® under an occlusive dressing at least 60 minutes before procedure; anaesthetic effect lasts 30 minutes – 2 hours after removal of medication; may cause temporary blanching and edema of the skin
- add to some injections, eg depot corticosteroids, to prevent pain and local irritation
- although marketed for IVRA, lignocaine is not usually used for this purpose

**Products**
- LIDOCAINE CREAM 2.5 % (AS HCL) + PRILOCAIN 2.5 % CREAM 30 GM TUBE (EMLA®)
- LIDOCAINE SPRAY 5 GM (AS BASE) + CETRIMIDE 0.03 GM 50 GM AEROSOL (LIGNOSOL®)
- LIDOCAINE VIAL 100 MG/VIAL (2 %) (AS HCL) WITH ADRENALINE 50 ML VIAL (XYLOCAINE ADRENALINE®)
- LIDOCAINE VIAL 100 MG/VIAL (2 %) (AS HCL) WITHOUT ADRENALINE 50 ML VIAL (LIDOCAINE®, LIDOCAIN®, LIDOCAINE RICHMOND®, LIDOCAINE HCL®, XYLOCAINE PLAIN®)

### 15.04 OPIOID ANALGESICS

**Mode of action**
Potent, short-acting mu-opioid receptor agonists and analogues of fentanyl.

**Specific considerations**
Severe respiratory compromise: further respiratory depression occurs; consider only if mechanical ventilation is to be used.
Debilitated or acutely ill patients: more sensitive to adverse and anaesthetic effects; reduce dose and monitor closely.
Elderly: Increased sensitivity to opioid effects; reduce initial dose and titrate to effect.
Pregnancy: May cause respiratory depression in the newborn if used during labour or before clamping of the cord during caesarean section; ADEC category C.
Breastfeeding: Safe to use.

**Adverse effects**
Common: respiratory depression, hypotension, bradycardia, muscle rigidity (including chest wall rigidity), postoperative shivering, itch
Rare: arrhythmias

**Comparative information**
Unlike other opioids (including alfentanil) which are metabolised in the liver, remifentanil is rapidly and extensively metabolised by nonspecific blood and tissue esterases. Therefore accumulation does not occur; and recovery remains rapid, predictable and without risk of recurrent respiratory depression.
Cardiovascular stability in response to laryngoscopic and surgical stimulation seems to be superior with remifentanil compared to alfentanil and fentanyl.

**Practice points**
- dose requirements vary with age and clinical condition of the patient; titrate carefully to clinical response
- respiratory depression, hypotension, bradycardia and muscle rigidity are dose- and rate-dependent and are therefore more likely with bolus administration; resolution occurs within minutes of stopping administration.

### ALFENTANYL

**Mode of action**
Potent, short-acting mu-opioid receptor agonists and analogues of fentanyl.

**Indications**
Opioid adjunct during induction and/or maintenance of anaesthesia.

**Contraindications**
Allergy to alfentanil or other fentanyl analogues.

**Specific considerations**
Hepatic impairment: Clearance may be reduced; decrease dose and titrate to effect.

**Dosage**
Spontaneous ventilation: IV bolus, initially up to 7 micrograms/kg over 30–60 seconds; give further doses of 2–3 micrograms/kg every 10–15 minutes as required.

Controlled ventilation: IV bolus, initially 20–50 micrograms/kg; give further doses of up to 15 micrograms/kg every 10–15 minutes as required.

IV infusion, initial loading dose 20–100 micrograms/kg over 10 minutes (doses at low end of range can be given as a bolus), followed by maintenance of 0.5–1 microgram/kg/minute.

**Practice points**
- alfentanil is marketed as an induction agent, but is not used for this purpose
- peak analgesic and respiratory depressant effects occur within 1–2 minutes of an injection; the duration of analgesia is dose-related but lasts up to 10 minutes after single IV bolus of the recommended dose
- continuous infusion is preferable for cases lasting >60 minutes
- to avoid postoperative respiratory depression, stop infusion 10 minutes before the end of surgery.

**Products**
ALFENTANYL AMPS 1 MG/AMP 2 ML AMP (RAPIFEN®)

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**FENTANYL**

**Mode of action**
Opioid analgesics mimic endogenous opioids by activating opioid receptors in the central and peripheral nervous systems to produce analgesia, respiratory depression, sedation and constipation. They prevent transmission of the pain impulse by acting pre- and post-synaptically in the spinal cord, and by modulating the descending inhibitory pathways from the brain. Cough suppression occurs in the medullary centre of the brain.

The affinity of individual opioid analgesics for receptors varies and opioids may act as pure agonists or partial agonists. Partial agonists demonstrate a 'ceiling response' above which an increase in dose does not produce an additional increase in effect.

**Indications**
- Acute pain.
- Opioid adjunct during general anaesthesia.
- Chronic pain (for patients intolerant of morphine).
- Breakthrough pain (lozenge, for patients with cancer stabilized on an opioid analgesic).
- Combination with bupivacaine: Epidural analgesia.
- Combination with ropivacaine: Epidural infusion for analgesia.

**Contraindications**
Significant respiratory disease (except respiratory indications above).
Comatose patients, unless near death.
Phaeochromocytoma (risk of pressor response due to histamine release which occurs with morphine and some other opioids); however, fentanyl or its derivatives may be used since they do not cause release of histamine.

**Specific considerations**
Bradyarrhythmias: may be exacerbated.
Renal impairment: Current evidence suggests that fentanyl has no active or toxic metabolites and may be used in severe impairment when other opioids are inappropriate..

Hepatic impairment: Liver disease does not preclude use of opioids but dose adjustment may be required.
Reduce dose and titrate carefully in severe hepatic disease as may precipitate coma.

Elderly: Opioid dose requirement decreases progressively with age. In the elderly, use a lower initial dose and titrate to effect. There is an increased risk of adverse effects including cognitive impairment and falls.

Children: Opioid use in children is usually initiated or recommended by specialists.

Neonates and infants up to approximately 12 months are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.

Pregnancy: Opioid analgesics may cause respiratory depression in the newborn; withdrawal effects may occur in neonates of dependent mothers; ADEC category C. Codeine is category A, but prolonged use near term by mother may also produce respiratory and/or withdrawal effects in the newborn.
Breastfeeding: Safe to use.

**Adverse effects**
Common: rash, erythema, itch (patch); bradycardia; may have a lower incidence of nausea, vomiting and constipation than other opioids
Rare: chest wall rigidity with rapid/very high IV doses
The most serious adverse effect of opioids; this is best judged by the degree of sedation; respiratory rate reduction is a late and unreliable indicator. Sedation is best monitored by using a sedation score, an example of which is given below:

**Sedation score:**
- 0 – none
- 1 – mild, occasionally drowsy, easy to rouse
- 2 – moderate, constantly drowsy (eg falls asleep while talking), easy to rouse
- 3 – severe, somnolent, difficult to rouse
- S – normal sleep.

Aim to keep the sedation score <2; a score of 2 represents early respiratory depression.

Nausea and vomiting: May occur initially; an antiemetic may be given prophylactically, but review use within a few days as nausea often lessens with continued opioid use.

Constipation: Occurs with chronic use; tolerance to this develops slowly, if at all. Attention to fluid intake, diet and mobility plus regular laxative use (eg senna, sorbitol) is essential as soon as opioids are started; there is no evidence to show that one type of laxative is superior to another.

Cognitive function: Effects on cognitive and psychomotor function are less clear, but are thought to be minimal for most patients receiving stable opioid doses chronically.

**Dosage**

**Anaesthesia:** Dosage varies with age and clinical condition of the patient.

**Adult**
Spontaneous ventilation, IV 50–100 micrograms, then 25–50 micrograms as required.
Assisted ventilation, IV 50 micrograms – 3.5 mg, then 50–200 micrograms or more as required.

**Child**
Spontaneous ventilation, IV 0.5–2 micrograms/kg, then 1 microgram/kg as required.
Assisted ventilation, IV 2–5 micrograms/kg, then 1–3 micrograms/kg as required. For longer procedures or if postoperative ventilation is planned (eg neurosurgery, cardiac surgery) use an initial dose of 10–20 micrograms/kg.

**Acute pain (including patient-controlled analgesia)**

**Transdermal:** Base dose on previous 24-hour opioid requirement; calculate equivalent 24-hour fentanyl dose if necessary. It may be appropriate to stabilize the patient on fentanyl SC infusion, and then convert to the patch which releases fentanyl at the same hourly rate as the infusion. Use 1 patch every 3 days.

**SC infusion:** Base dose on previous 24-hour opioid requirement; calculate equivalent 24-hour fentanyl dose.

**Breakthrough pain**
Lozenge, initial dose 200 micrograms, repeat in 30 minutes if required. If analgesia is inadequate after using this dose several times, titrate upwards through the available dosage strengths to an effective dose. If >4 breakthrough doses are required per day adjust the regular baseline opioid dose.

**Dose equivalence**

**Analgesic effect,** 100–150 micrograms fentanyl SC is approximately equivalent to 10 mg morphine IM/SC.

**Transdermal route,** the manufacturer states that 25 micrograms/hour patch is approximately equivalent to 90 mg/24 hours oral morphine.

Use the same dosage rate for transdermal patch and SC infusion.

**Patient counselling**

**Patch:** apply to dry, hairless, non-irritated skin on the upper part of your body or upper arm. Do not apply after a hot bath or shower. Do not use if patch is damaged or cut. Write the date and time it is applied on the patch with permanent marker. Remove after 3 days (72 hours) and put a new patch on a different place.

When wearing the patch, do not allow it to come into contact with direct sources of heat such as electric blankets, heat pads, heat lamps, saunas.

Lozenge: place in the mouth against the cheek and move it around the mouth using the applicator. Let it dissolve over a 15-minute period. Do not chew.

**Practice points**

**Transdermal**
do not use patch for postoperative and other acute pain because of the risk of life-threatening respiratory depression; it has a prolonged onset and duration of action; rapid and safe dose titration is not possible

patch is best reserved as an alternative to SC morphine for palliative care patients with stable opioid requirements who are unable to take oral morphine

do not cut or divide the patch as this may affect its release characteristics

patch takes about 24–72 hours to reach maximum effect; steady state concentration may not be reached until the second patch is applied; wean other analgesics slowly after first patch is applied

patch is effective for 72 hours; plasma concentration reduces slowly after the patch is removed (eg concentration is halved after about 17 hours)

monitor for adverse effects for up to 24 hours after removal of patch

heat increases the release of fentanyl from patch; monitor for increased adverse effects if patient is exposed to high ambient temperatures, external heat source (including heated blanket), or develops a fever

40–50% of the fentanyl dose remains in the patch after 3 days; this is a significant amount of fentanyl; to avoid illicit use dispose of patches by folding adhesive sides together and returning them to the pharmacy

Subcutaneous

SC fentanyl is not recommended for acute pain

SC fentanyl infusion may be used as an alternative to SC morphine in palliative care patients who develop morphine intolerance; the larger volumes of fentanyl required may necessitate more frequent changes of the SC infusion site

SC sufentanil (available under the SAS) may be used as an alternative to SC fentanyl for palliative care as a smaller volume of infusion is required

Oromucosal

fentanyl lozenges may be used for breakthrough pain in cancer patients already stabilized on an opioid

about 25% of the fentanyl is absorbed rapidly through the buccal mucosa and pain relief begins after 5–10 minutes; the rest of the drug is swallowed and absorbed more slowly, giving peak plasma concentration at 20–40 minutes

any partly used lozenges should be returned to the pharmacy to avoid illicit use

there is no dose equivalence between fentanyl lozenges and other opioid formulations (including fentanyl patches)

fentanyl or sufentanil injection is occasionally used sublingually for breakthrough pain in cancer patients receiving fentanyl or sufentanil infusion, or transdermal fentanyl; this is not an approved use and informed consent must be obtained from the patient

Products

FENTANYL AMPS 100 MCG/AMP (AS CITRATE) 2 ML AMP (FENTANYL®, FENTANYL CITRATE®)

FENTANYL AMPS 500 MCG/AMP (AS CITRATE) 10 ML AMP (FENTANYL®, FENTANYL CITRATE®)

FENTANYL PATCH 5 MG (AS CITRATE) (DUROGESIC®)

FENTANYL PATCH 7.5 MG (AS CITRATE) (DUROGESIC®)

FENTANYL PATCH 10 MG (AS CITRATE) (DUROGESIC®)

MORPHINE

Mode of action
See Fentanyl

Indications
Moderate-to-severe acute and chronic pain.
Acute pulmonary edema.
Relief of severe dyspnea, e.g. lung cancer, terminal COPD.
Cough suppression.
Diarrhea.

Specific considerations
Renal impairment: Morphine's active metabolites have a longer half-life than morphine and accumulate in the elderly and in renal impairment; may cause respiratory depression and delirium.
Moderate, chronic use requires lower doses; take into account adverse effects and need for adequate analgesia.
Severe, reduce dose; avoid chronic use due to accumulation of active metabolites.
Hepatic impairment: Severe, avoid use; may cause excessive sedation or coma.

Coexisting conditions
Uncorrected endocrine abnormalities, hypothyroidism, adrenocortical insufficiency, acute alcoholism, myasthenia gravis: careful titration of dose of opioids required.
Epilepsy or a recognised risk for seizure, eg head injury, metabolic disorders, alcohol and drug withdrawal, CNS infections: increased risk of seizure.
Untreated raised intracranial pressure: may be used for associated pain in palliative care; seek specialist advice.
Asthma during acute attack, unless ventilated: opioids depress respiration and cough reflex and dry secretions.
Hypotension, shock: reduced blood volume increases hypotensive risk; also impairs IM/SC absorption; careful titration of opioid dose required.
Biliary colic or surgery: all opioids, including pethidine and morphine, may cause spasm of sphincter of Oddi; there appears to be little difference in effect between the different opioids.
Renal impairment: Take extra care with continued use of codeine, dextropropoxyphene, hydromorphone, morphine and pethidine in patients with impaired renal function because of accumulation of active/toxic metabolites.
Adjust dose or use an alternative opioid, such as fentanyl. See Table 3–2 Opioid comparative information.
Hepatic impairment: Liver disease does not preclude use of opioids but dose adjustment may be required.
Reduce dose and titrate carefully in severe hepatic disease as may precipitate coma.
Elderly: Opioid dose requirement decreases progressively with age. In the elderly, use a lower initial dose and titrate to effect. There is an increased risk of adverse effects including cognitive impairment and falls.
Children: Opioid use in children is usually initiated or recommended by specialists.
Neonates and infants up to about 12 months of age are more susceptible to respiratory depression associated with opioid use. Start with a low dose and titrate to effect.
Pregnancy: Opioid analgesics may cause respiratory depression in the newborn; withdrawal effects may occur in neonates of dependent mothers; ADEC category C. Codeine is category A, but prolonged use near term by mother may also produce respiratory and/or withdrawal effects in the newborn.
Lactation: Safe to use.

**Adverse effects**
Common: nausea and vomiting, drowsiness, dizziness, headache, orthostatic hypotension, itch, dry mouth, miosis, urinary retention, constipation.
Infrequent: dose-related respiratory depression, confusion, hallucinations, delirium, urticaria, hypothermia, bradycardia or tachycardia, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses in palliative care), flushing due to histamine release (except fentanyl and remifentanil).
Rare: SIADH, anaphylaxis, seizure.

**Dosage**
Titrate dose to patient needs. In acute pain and palliative care there is no maximum dose; only adverse effects limit the morphine dose. In chronic non-cancer pain, involve a specialist pain team in assessing and managing the patient.
The following are approximate dose ranges for patients starting on opioids. Doses will vary widely depending on the indication, eg acute or chronic pain, and previous analgesic requirements.
Monitor cardiorespiratory status of patient closely, particularly with continuous infusion or repeated parenteral doses in opioid-naïve individuals.

**Acute pain, adult**
IV, initial dose
0.5–2 mg repeated every 3–5 minutes. This interval may not represent the true time to peak effect (which may be up to 15 minutes). Titrate dose according to response, respiratory rate and sedation score. Use the lower dose in patients >70 years of age.
SC/IM
Suggested doses are for opioid-naïve patients and may vary according to the clinical situation; start at lower end of dose range; titrate subsequent doses to the individual’s need.
20–39 years, 7.5–12.5 mg every 2 hours as required.
40–59 years, 5–10 mg every 2 hours as required.
60–69 years, 2.5–7.5 mg every 2 hours as required.
70–85 years, 2.5–5 mg every 2 hours as required.
>85 years, 2–3 mg every 2 hours as required.

**Acute pain, child**

**Neonate**
IV infusion, 10–20 micrograms/kg/hour.
Infant, child
IV, 50–100 micrograms/kg/dose every 4 hours.
IV infusion, 10–40 micrograms/kg/hour.
Patient-controlled analgesia
According to hospital or unit protocols.
Chronic cancer pain, adult
Initial dosing: Initial dose depends on previous opioid exposure:

- if opioid-naive, start with 2.5–5 mg oral liquid every 4 hours
- if previously on opioids, consider equivalent analgesic dose of morphine.
Oral liquid, 2.5–20 mg every 4 hours. Initial dose will depend on previous analgesia. Titrate doses to effect and calculate 24-hour morphine requirement.
Maintenance dosing: Convert the 24-hour dose of oral liquid into an equivalent dose of a controlled release product for maintenance treatment.
Oral controlled release tablet or controlled release liquid, total daily dose as determined for oral liquid, but give half total daily dose every 12 hours.
Oral controlled release capsule, total daily dose as determined for oral liquid; half total daily dose may be given every 12 hours or total daily dose every 24 hours; total daily dose every 24 hours.
SC infusion, calculate 24-hour oral dose of morphine and give one-third by SC infusion over 24 hours.
Chronic non-cancer pain, adult: Involve a specialist pain team in managing these patients. Start with the equivalent of controlled release morphine 5–30 mg twice daily and adjust dose according to the response after 1 week or less.
Use regular (by the clock) dosing. In general, avoid short acting preparations.
Breakthrough pain: Use additional doses of morphine liquid for breakthrough pain, using one-twelfth to one-sixth of the daily requirement given as frequently as required. If repeated breakthrough doses are required, adjust the regular baseline morphine dose.
Chronic cancer pain, infant and child: SC infusion, 30–60 micrograms/kg/hour.
Acute pulmonary edema: IV, 1–5 mg. Use lower end of dose range in the elderly.
Renal impairment: Moderate impairment, give three-quarters of estimated required dose. Severe impairment, give half of estimated dose and watch for excessive sedation; avoid chronic use.
Dose equivalence
For chronic dosing, 30 mg oral morphine is equivalent to 10 mg SC/IM/IV morphine. Use the same dose for sulfate, tartrate and hydrochloride salts.
Administration instructions
For IV use, dilute and give over 4–5 minutes.
Compatible fluids: sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%.
Controlled release capsules (Kapanol®) may be opened, and the pellets sprinkled on soft food or mixed with 30 mL of fluid and taken within 30 minutes. They may be mixed with 10 mL of water or liquid feed and given through a 16 gauge French gastrostomy tube, and rinsed through with further liquid to ensure all pellets are used. Do not crush or chew pellets.
Patient counselling
Controlled release tablets or capsules must not be crushed or chewed.
Practice points
- peak analgesia following a dose of morphine occurs:
  - within 60 minutes after conventional oral liquid
  - 30–60 minutes after SC/IM
  - 10–15 minutes after IV
  - 4–5 hours after controlled release tablet/capsule
  - 8–15 hours after controlled release capsule
- do not use controlled release preparations for acute pain management as slow onset and offset make rapid, safe titration impossible
- reassess the patient's pain frequently and adjust dose of morphine accordingly
- if morphine overdose occurs in severe renal impairment, naloxone infusion for several days may be necessary, see

Products
MORPHINE AMPS 10 MG/AMP (AS SULFATE) (MORPHINE SULPH®, MORPHINE SULPHATE®)
MORPHINE AMPS 15 MG/AMP (AS SULFATE) (MORPHINE SULPH®)

PETHIDINE
See Fentanyl
Indications
Obstetric analgesia.
Moderate-to-severe acute and chronic pain.
Relief of severe dyspnea, e.g. lung cancer, terminal COPD.

Contraindications
Renal impairment: Treatment with, or within 14 days of, a MAOI (including selegiline).
Significant respiratory disease (except respiratory indications above).
Comatose patients, unless near death.
Phaeochromocytoma.

Specific considerations
Treatment with drugs which can contribute to the serotonin syndrome: may increase likelihood of serotonin syndrome; avoid combinations or monitor clinical course carefully.
Elderly: Risk of norpethidine toxicity is increased in the elderly and in impaired renal function.

Adverse effects
Common: nausea and vomiting, drowsiness, dizziness, headache, orthostatic hypotension, itch, dry mouth, miosis, urinary retention, constipation.
Infrequent: dose-related respiratory depression, confusion, hallucinations, delirium, urticaria, hypothermia, bradycardia or tachycardia, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses in palliative care), flushing due to histamine release (except fentanyl and remifentanil).
Rare: SIADH, anaphylaxis, seizure.

Dosage
Acute pain, adult
IV, initial dose
5–20 mg repeated every 3–5 minutes. This interval may not represent the true time to peak effect (which may be up to 7 minutes). Titrate dose according to response, respiratory rate and sedation score. Use the lower dose in patients >70 years of age.
SC/IM
Starting doses are guidelines only and may vary according to the clinical situation; start at lower end of dose range; titrate subsequent doses to the individual’s need.
20–39 years, 75–125 mg every 2 hours as required.
40–59 years, 50–100 mg every 2 hours as required.
60–69 years, 25–75 mg every 2 hours as required.
70–85 years, 25–50 mg every 2 hours as required.
>85 years, 20–30 mg every 2 hours as required.
Suggested maximum in young adults is 1000 mg in first 24 hours, then 600 mg daily; use for a maximum of 72 hours.
Acute pain, child: IM/IV/SC, 0.5–2 mg/kg/dose every 2–4 hours (maximum 10 mg/kg/day).
Patient-controlled analgesia: According to hospital or specialist unit protocols.
Obstetric analgesia: IM, 50–100 mg initially; may be repeated after 1–3 hours; maximum 400 mg in 24 hours. Do not use within 2 hours of anticipated delivery.
Severe hepatic impairment: Decrease dose by half to three-quarters.
Dose equivalence: 100 mg oral is equivalent to 25–50 mg IV/IM/SC. Avoid oral route.

Practice points
• since pethidine has no advantages, it is not recommended if multiple doses are needed
• do not use naloxone for norpethidine toxicity; it may exacerbate problems (antagonises sedative but not excitatory effects of norpethidine)
• rarely appropriate for premedication
• inappropriate for treatment of migraine, as has a short duration of effect, and is associated with drug-seeking behaviour
• pethidine seems to be preferred to morphine or methadone by recreational or illicit drug users

Products
PETHIDINE AMPS 50 MG/AMP (AS HCL) 1 ML AMP (PETHIDINE®, PETHIDINE B.P®)
PETHIDINE AMPS 100 MG/AMP (AS HCL) 2 ML AMP (PETHIDINE®, PETHIDINE B.P®)

REMIFENTANIL
Mode of action
A potent mu-opioid receptor agonist and analogue of fentanyl.
**Indications**
Opioid adjunct during induction and/or maintenance of anaesthesia for all surgical procedures in adults.
Opioid adjunct during induction and/or maintenance of anaesthesia during surgical (except cardiac) procedures in children >1 year.
Short term postoperative analgesia after cardiac surgery in adults.
Analgesia and sedation for ventilated patients in intensive care.

**Contraindications**
Allergy to remifentanil or other fentanyl analogues.
Epidural or intrathecal use.

**Specific considerations**
Severe respiratory compromise: further respiratory depression occurs; consider only if mechanical ventilation is to be used.
Elderly: Increased sensitivity to opioid effects: reduce dose by half and titrate carefully.
Pregnancy: Inadequate data; ADEC category C.
Lactation: No data.

**Adverse effects**
Common: hypotension, bradycardia, muscle rigidity (including chest wall rigidity), postoperative shivering, itch.
Rare: cardiac arrhythmias, anaphylactoid/anaphylactic reactions.

**Dosage**
**Adult**
**Induction**
IV bolus, 1 microgram/kg over 60 seconds.
IV infusion, 0.5–1 microgram/kg/minute.
If endotracheal intubation is to be performed >8–10 minutes after starting the IV infusion, the bolus injection is not necessary.
**Maintenance**
IV bolus, 0.5–1 microgram/kg over 30–60 seconds, give every 2–5 minutes as required.
IV infusion, 0.05–2 micrograms/kg/minute, adjust every 2–5 minutes according to response.
**Spontaneous ventilation**
IV infusion, 0.04 microgram/kg/minute initially with titration to effect, then 0.025–0.1 microgram/kg/minute.
**Use in intensive care**
IV infusion, 0.1–0.15 microgram/kg/minute initially, titrate to effect in increments of 0.025 microgram/kg/minute allowing at least 5 minutes between dose changes; maintenance range 0.006–0.74 microgram/kg/minute.
**Elderly**: Halve dose.
**Child >1 year**
**Induction**
IV bolus, 1 microgram/kg over 60 seconds.
IV infusion, 0.05–0.5 microgram/kg/minute.
If endotracheal intubation is to be performed >8–10 minutes after starting the IV infusion, the bolus injection is not necessary.
**Maintenance**
IV bolus, 0.5–1 microgram/kg over 30–60 seconds, give every 2–5 minutes as required.
IV infusion, 0.05–0.5 microgram/kg/minute, adjust every 2–5 minutes according to response.

**Practice points**
- in common with other opioids, remifentanil is not indicated for use as the sole agent for induction of anaesthesia; loss of consciousness cannot be assured and the required doses result in a high incidence of muscle rigidity
- hypotension, bradycardia and muscle rigidity are dose- and rate-dependent and are therefore more likely with bolus administration; resolution occurs within minutes of stopping administration
- remifentanil is rapidly and extensively metabolised by nonspecific esterases in blood and tissues; it is not a substrate for plasma cholinesterase
- peak hemodynamic effects occur within 3–5 minutes of a single dose or infusion rate increase
- recovery from its effects occurs within 5–10 minutes; new steady state concentrations occur within 5–10 minutes after alteration in infusion rate
• duration of action at a given dose does not increase with increasing duration of administration, owing to lack of drug accumulation; recovery remains rapid, predictable and without risk of recurrent respiratory depression
• because of its rapid offset of action, appropriate analgesia for the management of postoperative pain should be given before stopping remifentanil
• analgesic potency is similar to that of fentanyl but there is greater attenuation of the hemodynamic response to endotracheal intubation with remifentanil
• used by specialist anaesthetists in children <1 year during induction and maintenance of anaesthesia; caution and careful monitoring required as clearance is highly variable in these children
• also used for conscious sedation in adults, although not a marketed indication

**Products**

REMIFENTANIL VIAL 1 MG/VIAL  1 ML VIAL (ULTIVA®)
REMIFENTANIL VIAL 2 MG/VIAL  2 ML VIAL (ULTIVA®)

### 15.06 SKELETAL MUSCLE RELAXANT

**DANTROLENE**

**Mode of action**
A direct acting skeletal muscle relaxant. Decreases muscle contraction by interfering with calcium release from sarcoplasmic reticulum.

**Indications**
Chronic spasticity associated with spinal cord injury, head injury, multiple sclerosis, cerebral palsy or stroke (oral)
Malignant hyperthermia (IV).

**Contraindications**
Active hepatic disease (eg hepatitis, cirrhosis).

**Specific considerations**
History of hepatic disease: increased risk of hepatotoxicity.
Impaired cardiac or pulmonary function: increased risk of exacerbation.
Treatment with oestrogens: may increase risk of hepatotoxicity in women >35 years; use combination cautiously.
Renal impairment: May require dose reduction.
Children: Safety not established in children <5 years.
Pregnancy: Limited data available; ADEC category B2.
Lactation: No data available; avoid use.

**Adverse effects**
drowsiness, dizziness, fatigue, diarrhea, nausea, vomiting, anorexia, constipation, elevated hepatic enzymes, hepatitis (dose-related), rash, unstable BP, tachycardia, dyspnea, cardiac failure, enuresis, urinary retention, headache, insomnia, nervousness, confusion, depression, visual disturbances, aplastic anaemia, leucopenia, lymphocytic lymphoma, seizures, pleural effusion with pericarditis (IV).

**Dosage**
Chronic spasticity
Adult, oral, initially 25 mg once daily, increase to 25 mg 2–4 times daily, and then by 25 mg increments up to 50 mg 2–4 times daily according to response. Maximum, 400 mg daily.
Child, oral, initially 0.5 mg/kg twice daily, increased to 0.5 mg/kg 3–4 times daily, and then by increments up to 2 mg/kg 3 times daily according to response. Maximum, 200 mg daily.
Malignant hyperthermia: IV, initially 1 mg/kg repeated every 1–2 minutes until symptoms subside, or to a maximum cumulative dose of 10 mg/kg.

**Practice points**
Chronic spasticity
• stop treatment if no benefit is apparent within 4–6 weeks
• adverse effects usually occur at start of treatment and can be minimized by beginning treatment at a low dose and increasing dosage gradually
• stop treatment if diarrhea is severe; if it recurs upon readministration, stop treatment permanently
• monitor liver function at the beginning of treatment and at intervals of 1–2 months; stop treatment if there are persistent abnormalities in liver function tests.
15.07 ANTAGONISTS FOR CENTRAL AND RESPIRATORY DEPRESSION

FLUMAZENIL

Mode of action
Competitive antagonist at benzodiazepine receptors.

Indications
Marketed: Reversal of benzodiazepine sedation used for anaesthesia; Benzodiazepine overdose or intoxication (rarely indicated).
Accepted: Hepatic encephalopathy.

Specific considerations
Mixed overdoses: using flumazenil to reverse benzodiazepine effects in mixed overdoses of benzodiazepines and proconvulsant drugs (eg TCA, chloral hydrate, theophylline, antihistamines, amphetamines) may be dangerous, resulting in uncontrollable seizures and death. A negative history of ingestion of proconvulsant drugs, normal ECG and no physical signs of anticholinergic or sympathomimetic drug overdose make such co-ingestion unlikely.
Benzodiazepine dependence: rapid reversal of benzodiazepine effects may be undesirable in people with benzodiazepine dependence as it may precipitate severe withdrawal symptoms and seizures.
Severe head injury, unstable intracranial pressure: if treated with flumazenil to reverse effects of benzodiazepines, may alter cerebral blood flow, cause raised intracranial pressure, or convulsions.
Pregnancy: Do not use; risk of precipitating withdrawal in fetus; ADEC category B3.
Lactation: No data available.

Adverse effects
Common: nausea, vomiting.
Infrequent: people with benzodiazepine dependence may have anxiety, agitation, confusion and seizures.

Dosage
Benzodiazepine overdose
Adult, initially 0.3–1 mg IV, repeated as necessary to a total of 2 mg.
Maintenance dose (if indicated), half the initial dose needed to waken the patient given every hour by continuous infusion (0.1–0.4 mg/hour).
Elderly, initially 0.1 mg IV.

Postoperative reversal of benzodiazepine sedation
Adult, 0.2–0.5 mg IV to reduce sedation.
Child, 5 micrograms/kg IV, repeated every 60 seconds to a total of 40 micrograms/kg (maximum 2 mg), then 2–10 micrograms/kg/hour if required.

Practice points
- benzodiazepine overdose is not usually of major clinical significance and flumazenil treatment is rarely indicated; may be required to avoid intubation and/or intensive care admission
- the half-life of flumazenil (about 1 hour) is much shorter than that of all benzodiazepines; repeat doses of flumazenil would be required to maintain effect.

Products
FLUMAZENIL VIAL 500 MCG/VIAL  5 ML VIAL (ANEXATE®, FLUNEXATE®)

NALOXONE

Mode of action
Competitive antagonist at opioid receptors.

Indications
Marketed: Opioid overdose or intoxication:
- as a diagnostic aid in suspected overdose
- to avoid the need for assisted ventilation in opioid overdose

Reversal of opioid sedation used for anaesthesia:
- as an aid to weaning from assisted ventilation in intensive care units
• to reverse sedation after short diagnostic procedures

Reversal of sedation and respiratory depression in neonates where there has been maternal exposure to opioids.

Accepted: To confirm patient is opioid free before use of naltrexone.

Specific considerations
Opioid dependence: rapid reversal of opioid effects may lead to an acute withdrawal syndrome.
Renal impairment: Excretion of some opioids and/or their active metabolites (codeine, dextropropoxyphene, dihydrocodeine, morphine, pethidine, oxycodone) is delayed and they will accumulate; extended treatment including naloxone infusion may be required to reverse opioid effect.

Pregnancy: Do not use in opioid-dependent women during pregnancy; risk of withdrawal in fetus; ADEC category B1.

Lactation: May be used.

Adverse effects
Common: people with opioid dependence may have an acute withdrawal syndrome, eg anxiety, agitation, tachycardia, confusion.
Rare: opioid-dependent people may occasionally have more severe effects, eg seizures, pulmonary edema, ventricular arrhythmias.

Dosage
Opioid overdose
Adult, child, 400–800 micrograms IV/IM/SC repeated as necessary; larger initial doses may be required—be guided by pupil size and clinical response. If the diagnosis of opioid poisoning is correct, the patient should improve in 1 minute. Maintenance dose (if indicated): two-thirds of the dose needed to waken the patient, given each hour by continuous infusion, with further titration as required.

Neonate, 100 micrograms/kg IV/IM/SC (maximum 2 mg), repeated as necessary; or infusion at 10 micrograms/kg/hour, titrated to response.

Postoperative reversal of opioid sedation
Adult, 100–200 micrograms IV to reduce sedation, repeated as necessary.
Child, 5–10 micrograms/kg IV, repeated as necessary.

To confirm patient is opioid free (naloxone challenge)
Observe for withdrawal symptoms: piloerection, restlessness, rhinorrhoea, yawning, sweating, lacrimation, vomiting.

IV, initially 200 micrograms, observe for withdrawal reactions for 30 seconds, then inject 600 micrograms and observe for 5 minutes.

IM, initially 400 micrograms, if no reaction after 10 minutes give another 400 micrograms and observe for 10 minutes.

Practice points
• oxygen and ventilatory support should be the first treatment priority in opioid overdose or opioid sedation
• repeat doses or infusion of naloxone may be required, especially with longer acting opioids and those with active metabolites (methadone, diphenoxylate, codeine, dextropropoxyphene), to maintain effect as the half-life of naloxone is <1 hour (shorter than all the opioids)
• observe patients who respond to naloxone for 2–3 hours after naloxone is ceased to ensure they do not relapse; this is especially important in methadone overdose or controlled release opioid preparation overdose, when narcosis may persist for >24 hours
• use of naloxone in opioid overdose is not always necessary; restrict its use to situations where diagnosis is unclear or when there is a need to protect the airway or maintain adequate respiration
• response to naloxone is rapid; repeated small doses may be given every minute if there is no response up to a total dose of 2 mg; higher doses are occasionally necessary in overdoses of partial opioid agonists (eg buprenorphine); however, failure to respond to 2 mg usually indicates another cause of unconsciousness
• naloxone does not reverse other toxic effects of opioids (eg cardiac arrhythmias due to nordextropropoxyphene, seizures due to norpethidine)
• do not give naloxone to babies of mothers who have been taking methadone or heroin.

Products
NALOXONE AMPS 0.04 MG/AMP (AS HCL) 2 ML AMP (NAXONE®)
NALOXONE AMPS 0.40 MG/AMP (AS HCL) 1 ML AMP (NAXONE®)

15.08 MISCELLANEOUS
ATROPINE

Mode of action
Atropine competitively inhibits binding of acetylcholine to muscarinic receptors in the parasympathetic and central nervous systems. In normal circumstances atropine increases heart rate, causes mydriasis, inhibits smooth muscle contraction in the GI and genitourinary systems and inhibits secretion from a variety of glands.

When there is excessive acetylcholine, eg in organophosphate poisoning, the muscarinic effects of poisoning (eg miosis, salivation, sweating, bradycardia, vomiting and diarrhea) are reversed by atropine.

Indications
- Bradycardia with hemodynamic compromise, asystole.
- Organophosphate poisoning:
  - for diagnostic use to determine if there is significant organophosphate exposure
  - for treatment when significant muscarinic effects are evident

Premedication for anaesthetic procedures
- Coadministration with anticholinesterases (eg neostigmine) used to reverse neuromuscular blockade (to block muscarinic effects).

Contraindications
- If atropine is needed for treatment of organophosphate poisoning, contraindications are relative.
- Closed angle glaucoma.
- Severe inflammatory GI disease or GI obstruction.
- Prostatism and urinary obstruction.
- Myasthenia gravis.

Specific considerations
- Constipation, delirium, tachycardia, fever (from any cause): may be worsened by atropine.
- Pregnancy: Safe to use; ADEC category A.
- Lactation: Safe to use.

Adverse effects
- Common: dry mouth, tachycardia, blurred vision, photophobia, constipation, urinary retention, flushing, delirium, fever.
- Infrequent: vomiting, headache, paralytic ileus, rash.
- Rare: closed angle glaucoma, seizures.

Dosage
- Premedication
  - Adult, initially 0.3–0.6 mg IV/IM.
  - Child, initially 0.01–0.02 mg/kg IV/IM.
- Coadministration with anticholinesterases after surgery
  - Adult, initially 0.6–1.2 mg IV.
  - Child, initially 0.02 mg/kg IV.
- Anticholinesterase (eg organophosphate) poisoning
  - If atropine is required for organophosphate poisoning pralidoxime should also be given.
  - Adult, initial, 1–2 mg IV repeated every 5–10 minutes as necessary until patient is atropinised (should abolish all secretions), then infusion titrated against clinical effects.
  - Child, 0.05 mg/kg IV every 5–10 minutes until atropinisation is observed.

Because atropine is a competitive inhibitor, high doses may be required in severe poisoning and use in these circumstances can be complicated; seek advice from a Poisons Information Centre, telephone 13 11 26.

Practice points
- a single dose of up to 1.2 mg is generally sufficient for maximal therapeutic effect as a premedication and for bradycardia in most patients; increasing the dose in patients who fail to respond is not helpful
- atropine tablets are not as effective as IV atropine, which is almost always required for significant organophosphate poisoning.

Products
ATROPINE AMPS 1,000 MCG/AMP 1 ML AMP (NOT REGISTERED)

NEOSTIGMINE

Mode of action
Reduces breakdown of neuronally released acetylcholine by inhibiting cholinesterase; enhances neuromuscular transmission in skeletal and smooth muscles.
**Indications**
Myasthenia gravis.
Reversal of neuromuscular blockade induced by non-depolarising neuromuscular blockers.

**Contraindications**
Intestinal or urinary obstruction.

**Specific considerations**
Asthma, cardiovascular disorders (including arrhythmia, bradycardia, hypotension), seizures, Parkinson's disease, peptic ulcer: risk of aggravation.
Renal impairment: Requires dose reduction.
Pregnancy: Seek specialist advice; neostigmine ADEC category B2, pyridostigmine ADEC category C.
Lactation: Safe to use; monitor infant for muscular weakness.

**Adverse effects**
Common: increased salivation, nausea, vomiting, diarrhea, abdominal cramps.
Infrequent: rash, anaphylaxis.

Overtreatment: May lead to a cholinergic crisis with increased cholinergic effects (eg excessive sweating, miosis, involuntary defecation and urination, nystagmus, bradycardia, hypotension, increased muscle weakness leading to fasciculation and paralysis), CNS effects (eg ataxia, convulsions, agitation, coma) and death due to respiratory failure or cardiac arrest.

Distinction between a cholinergic crisis (overtreatment) and a myasthenic crisis (undertreatment) may be difficult (especially if an anticholinergic drug is used to relieve adverse effects), and may require an edrophonium test.

**Dosage**
Myasthenia gravis
Adult, SC/IM 1–2.5 mg at suitable intervals during the day. Usual total daily dose, 5–20 mg.
Child, SC/IM 200–500 micrograms as required.
Neonate, SC/IM 50–250 micrograms every 2–4 hours 30 minutes before feeding.

Reversal of neuromuscular blockade
Adult, IV 50–70 micrograms/kg, up to 5 mg (with or after atropine 0.6–1.2 mg).
Child, IV 50 micrograms/kg/dose, up to 2.5 mg (with or after atropine 0.02 mg/kg).

**Practice points**
- for reversal of neuromuscular blockade, give neostigmine and atropine simultaneously, except for people with bradycardia who should be given atropine first to increase heart rate above 80 beats/minute
- neostigmine is still marketed for prevention and treatment of postoperative urinary retention and intestinal atony, but should not be used for these indications.

**Products**
NEOSTIGMINE AMPS 2.5 MG/AMPS (AS METHYL SULFATE) 1 ML AMP (NEOSTIGMINE®)

**PHENYLEPHRINE**
See Adrenaline

**Mode of action**
Phenylephrine hydrochloride is a sympathomimetic with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without significant stimulating effects on the CNS at usual doses. Its pressor activity is weaker than that of noradrenaline but of longer duration. After injection it produces peripheral vasoconstriction and increased arterial pressure; it also causes reflex bradycardia. It reduces blood flow to the skin and to the kidneys.

**indications**
Phenylephrine has been used parenterally in the treatment of hypotensive states, such as those encountered during circulatory failure or spinal anaesthesia.
An adjunct to local anaesthetics.

**Adverse effects**
Anxiety, tremor, tachycardia, headache, cold extremities.
Over dose: arrhythmias, cerebral hemorrhage, pulmonary edema.
Rare: nausea, vomiting, sweating, weakness, dizziness and hyperglycemia.

**Dosage**
For hypotension, an initial dose of phenylephrine hydrochloride 2 to 5 mg may be given as a 1% solution subcutaneously or intramuscularly with further doses of 1 to 10 mg if necessary, according to response.
In severe hypotensive states, 10 mg in 500 mL of glucose 5% or sodium chloride 0.9% has been infused intravenously, initially at a rate of up to 180 micrograms/minute, reduced, according to the response, to 30 to 60 micrograms/minute.

Products
PHENYLEPHRINE AMPS 1 % (AS HCL) 1 ML AMP (NEO-SYNEPHARINE®)
### Table 15.01 Comparison of inhalational anaesthetics

<table>
<thead>
<tr>
<th>Effect in fit patients</th>
<th>Desflurane</th>
<th>Isoflurane</th>
<th>Nitrous oxide</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>potency</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>blood:gas solubility*</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>airway irritation</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>respiratory rate</td>
<td>↑</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>myocardial depression</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>BP reduction</td>
<td>+</td>
<td>++</td>
<td>←→</td>
<td>+</td>
</tr>
<tr>
<td>heart rate</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>systemic vascular resistance</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>cardiac output</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prolongation of neuromuscular block</td>
<td>++++</td>
<td>++++</td>
<td>←→</td>
<td>+++</td>
</tr>
</tbody>
</table>

*low blood:gas solubility allows faster induction, quicker alteration in depth of anaesthesia and more rapid recovery

### Table 15.02 Comparison of non-depolarising neuromuscular blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset (minutes)1,2</th>
<th>Duration of action (minutes)1 initial dose</th>
<th>Histamine release3</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>atracurium</td>
<td>1.5</td>
<td>30–40</td>
<td>15–25</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no effect on heart rate4 can be used in renal or hepatic impairment</td>
</tr>
<tr>
<td>cisatracurium</td>
<td>2</td>
<td>30–40</td>
<td>20</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no effect on heart rate4 can be used in renal or hepatic impairment</td>
</tr>
<tr>
<td>mivacurium</td>
<td>2–2.5</td>
<td>15–30</td>
<td>15</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vagolytic and sympathomimetic effects (tachycardia, hypertension) prolonged action in severe renal or hepatic impairment</td>
</tr>
<tr>
<td>pancuronium</td>
<td>1.5–2.5</td>
<td>60–120</td>
<td>25–60</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>prolonged action in severe renal or hepatic impairment may cause tachycardia at high doses</td>
</tr>
<tr>
<td>rocuronium</td>
<td>1</td>
<td>30–40</td>
<td>15–20</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no effect on heart rate4 prolonged action in severe renal or hepatic impairment</td>
</tr>
<tr>
<td>vecuronium</td>
<td>2–3</td>
<td>20–40</td>
<td>20–40</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>prolonged action in severe renal or hepatic impairment</td>
</tr>
</tbody>
</table>

1onset and duration of action are dose-related; times given are for recommended doses
2time to satisfactory intubating conditions
3can cause flushing, hypotension, tachycardia, bronchospasm and rarely anaphylactoid reactions
4will not counteract bradycardia produced by many anaesthetics or by vagal stimulation during surgery; bradycardia may be more common with these drugs
### Table 15.03 Dose, onset and duration of action of local anaesthetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum dose1</th>
<th>Average onset of action (minutes)</th>
<th>Average duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without</td>
<td>with</td>
<td>topical and/or infiltration nerve blockade2</td>
</tr>
<tr>
<td>amethocaine</td>
<td>1 mg/kg</td>
<td>2 mg/kg</td>
<td>30–60</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>2 mg/kg</td>
<td>2 mg/kg</td>
<td>10–15</td>
</tr>
<tr>
<td>cocaine</td>
<td>1.5 mg/kg</td>
<td>1–5</td>
<td>1–5</td>
</tr>
<tr>
<td>levobupivacaine</td>
<td>2 mg/kg</td>
<td>10–15</td>
<td>15–30</td>
</tr>
<tr>
<td>lignocaine</td>
<td>3 mg/kg</td>
<td>7 mg/kg</td>
<td>5–10</td>
</tr>
<tr>
<td>mepivacaine</td>
<td>5–7 mg/kg</td>
<td>5–10</td>
<td>5–15</td>
</tr>
<tr>
<td>prilocaine</td>
<td>6 mg/kg</td>
<td>8 mg/kg</td>
<td>5–10</td>
</tr>
<tr>
<td>procaine</td>
<td>8 mg/kg</td>
<td>10–15</td>
<td>15–30</td>
</tr>
<tr>
<td>ropivacaine</td>
<td>3 mg/kg</td>
<td>10–15</td>
<td>15–30</td>
</tr>
</tbody>
</table>

1 when given as a single dose; doses given are guidelines only (see Dosage)

2 Onset of action of nerve blockade also depends on size of nerve; complete blockade takes longer with larger nerves

3 Only available as dental cartridge
CHAPTER 17 DIAGNOSTICS

17.01 RADIOCONTRAST MEDIA

CHOICE OF RADIOGRAPHIC CONTRAST MEDIUM

Radiographic contrast media contain elements with high atomic numbers that absorb X-rays. The agents most commonly used are iodinated organic compounds, whose degree of opacity or radiodensity is directly proportional to their iodine content. Barium sulfate is a metal salt with a long established use as a contrast medium. Other heavy atoms have been investigated, but many, such as thorium dioxide and tantalum, were unsuitable due to acute or chronic toxicity.

The iodinated contrast media may be classified as either ionic or nonionic, and additionally as monomeric or dimeric. The ionic monomeric media, such as the amidotrizoates, iomamide, and iopanoic acid, generally have very high osmolality when given in concentrations suitable for radiographic visualisation and the resulting hypertonic solutions are associated with a relatively high incidence of adverse effects. Since radiodensity depends solely upon the iodine concentration, and osmolality solely upon the number of particles present in a given weight of solvent, the osmolality of contrast medium solutions can be reduced for a given radiodensity by using an ionic dimeric medium, such as adipiodone or ioxaglic acid, that contains twice the number of iodine atoms in each molecule, or by using a nonionic medium that does not dissociate into cation and anion. Nonionic media may be monomeric, such as iohexol, iopamidol, iopromide, and ioversol, or dimeric, for example iotrolan. Thus the best ratio of radiodensity to osmolality is achieved with the nonionic dimeric media.

Radiographic techniques to visualise particular structures within the body depend upon the physical and chemical properties of the contrast medium used and upon the way in which it is administered. Some radiographic procedures and the specific contrast media used in them are described below. The likelihood of adverse effects is greater with the older iodinated ionic contrast media, especially in high risk patients, and this also influences the choice of contrast medium.

For urography (visualisation of the kidneys and urinary tract) the molecule must be small and highly water-soluble, with low protein-binding, so that glomerular filtration is encouraged with subsequent passage through the urinary tract. For good visualisation high concentrations must be achieved in the urinary tract from the start, and this in turn means high plasma concentrations: contrast media for urography are thus invariably given by the intravenous route. Examples of ionic urographic media include the amidotrizoates, iointalmates, and metrizoates. These ionic monomeric media have a relatively high incidence of adverse effects, due in part to their high osmolality, and better tolerance may be achieved with compounds of lower osmolality, such as ionic dimeric media (ioxaglic acid) and nonionic media (iohexol, iopamidol, and iopromide).

The requirements for angiography (visualisation of the circulatory system) are similar to those for urography in that a water-soluble molecule is required that can be readily distributed through the blood vessels. In addition, the solution should be of low viscosity to facilitate rapid injection and of high radiodensity to counteract the diluting effects of the blood. There are no particular differences between requirements for visualisation of veins (phlebography or venography) and those for arteries (arteriography); however, for angiocardiography (visualisation of the heart and heart vessels), or digital subtraction angiography where movement of a bolus of contrast medium through the circulation is studied over a period of time, the heart may be exposed to higher-than-usual concentrations of contrast medium and low cardiotoxicity is particularly important. There has been a general trend towards the use of low osmolality media for all types of angiography, since greatly improved tolerance, and in particular less pain on injection, means that procedures can be carried out without general anaesthesia and with less risk of serious adverse effects. Examples of angiographic media include iodixanol, iohexol, iopamidol, iopromide, and ioversol.

For gastrointestinal radiography the principal requirements are that the contrast medium should not be absorbed but should form an even, homogeneous coat on the gastrointestinal mucosa, without interacting with gut secretions or producing misleading radiographic artifacts. The chief contrast medium for this purpose is barium sulfate, and much effort has been devoted to the production of suitable formulations to improve its coating properties and reduce the formation of bubbles, cracks, and other radiographic artifacts.

The requirements for cholecystography and cholangiography (visualisation of the gallbladder and biliary tract) depend to some degree on the intended route of administration. In order that the molecule should be preferentially excreted in the bile it should be sufficiently large for biliary excretion and must possess a free carboxy or other acidic group, since the biliary active transport mechanism is an anion transfer process. In addition, the molecule should be protected by virtue of its size or by protein binding from the more rapid renal excretion processes. However, the oral cholecystographic agents need to be absorbed from the gastrointestinal tract before they become effective, and this
imposes a second, and to some extent conflicting, set of requirements. For optimal enteral absorption, molecules should be of relatively small size, sufficiently soluble in gastrointestinal fluids, and sufficiently lipophilic to pass the cell membranes of the mucosa. Examples of oral cholecystographic media include the iodoplates, iocetic acid, iopanoic acid, and sodium tyropanoate. These are relatively small, monomeric molecules and therefore they require conjugation with glucuronic acid within the body to achieve sufficient molecular weight for biliary excretion. They are often given after a fatty meal to enhance absorption and reduce the incidence of inadequate visualisation. The intravenous cholecystographic agents do not have to meet the above requirements for enteral absorption and are mostly larger, dimeric molecules that do not require conjugation. They are generally more effective than the oral media. Examples of intravenous cholecystographic media include salts of adipiodone and iotroxic acid.

For myelography (visualisation of the structures of the spinal cord) no special requirements other than good tolerance are necessary. Although visualisation was at one time achieved with oily media such as iofendylate these have now mostly been replaced with nonionic water-soluble media. These offer improved tolerance, better visualisation since they are miscible with cerebrospinal fluid, and, unlike the oil-based media, are removed from the subarachnoid space by normal pharmacokinetic mechanisms. Examples include iohexol and iopamidol.

Arthrography (visualisation of the joint capsule) may be performed with many different contrast media provided they are well-diluted before use.

Bronchography (examination of the bronchial tree) has been performed with oily or aqueous media, such as iopydol or ioprodine, instilled through a catheter or bronchoscope to coat the airways.

For hysterosalpingography (visualisation of the uterus and fallopian tubes) a water-soluble contrast medium is required. Examples include iotrolan, ioxaglic acid, and metrizoic acid.

Very high radiodensity is required to obtain good visualisation of the lymphatic structures in radiography of the lymphatic system (lymphography or lymphangiography). In addition, water-soluble media rapidly leave the system and only particulate or water-insoluble media or very large molecules persist within the lymphatic vessels for any length of time. The medium that has been most frequently used is iodised oil. It gives good visualisation of that part of the lymphatic system between the point at which it is infused and the point at which it enters the general circulation, but it is not distributed throughout the whole lymphatic space and has the potential for a number of severe side-effects.

**Adverse effects.**

Many of the adverse effects of iodinated ionic contrast media are associated with their high osmolality, reducing the osmolality through altering the ionic or molecular profile produces a reduced incidence of adverse effects. The newer nonionic, low-osmolar contrast media have a lower incidence of adverse effects than the older ionic, high-osmolar agents. The route and speed of administration, and the volume, concentration, and viscosity of the solution also affect the incidence of adverse effects. Most reactions occur within 5 to 10 minutes of injection, but they may be delayed. Hyperthyroidism has been reported following administration of iodinated contrast media, presumably due to small amounts of iodine present as a contaminant or released by any breakdown of the medium in the body. When given by injection the iodinated contrast media may cause nausea, a metallic taste, vomiting, flushing and sensations of heat, weakness, dizziness, headache, coughing, rhinitis, sweating, sneezing, lachrymation, visual disturbances, pruritus, salivary gland enlargement, pallor, tachycardia, bradycardia, transient ECG abnormalities, haemodynamic disturbances, and hypotension. Rarely, more severe adverse effects, including convulsions, paralysis, coma, rigors, ventricular fibrillation, pulmonary oedema, circulatory failure, and cardiac arrest have occurred. Occasionally anaphylactoid or hypersensitivity reactions occur; dyspnoea, bronchospasm, angioedema, and severe urticaria have been reported, and reactions have sometimes been fatal. Injection of amidotrizoates into the CNS produces severe neurotoxicity. Deaths have also been recorded due to acute renal failure, which may follow intravenous administration, particularly in dehydrated patients and patients with other predisposing factors.

Pain may occur at the injection site; extravasation may be followed by tissue damage, thrombophlebitis, thrombosis, venospasm, and embolism. Fibrinolysis and a possible depressant effect on blood coagulation factors has been reported. Disseminated intravascular coagulation has occurred. Meglumine salts are reportedly better tolerated and produce less pain on injection than sodium salts, but the sodium salts may be associated with a lower incidence of arrhythmias. As a result, the sodium and meglumine salts are often given in combination to minimise adverse effects. Mild diarrhoea may follow the oral or rectal use of sodium and meglumine amidotrizoates for gastrointestinal examinations. The accidental aspiration of solutions of these salts has caused fatal pulmonary oedema. Adverse effects are treated symptomatically and adequate resuscitative facilities should be available when radiographic procedures are to be employed.

Cost considerations mean that low-osmolar media tend to be reserved for patients considered to be at high risk.

**Adverse effects**
**Hypersensitivity**
Anaphylactoid reactions to iodinated contrast media are more common with the ionic agents than the nonionic media of lower osmolality. Patients at increased risk are those with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to a contrast medium, and those receiving beta blockers or interleukin-2 therapy. In such patients, nonionic media are preferred. Discontinuation of beta blockers should be considered in patients with other risk factors. Pretreatment with corticosteroids may be considered for preventing anaphylactoid reactions in high-risk patients and an antihistamine may be given. However, the value is uncertain.

**Thromboembolism**
Angiography is associated with a risk of thromboembolism. Contrast media have differing effects on coagulation, and choice of contrast medium may therefore affect this risk. Although nonionic media may be preferred in angiography due to their better tolerability, it has been suggested that they may contribute to the risk of thromboembolism since they have less anticoagulant activity than the ionic contrast media. Mixing of blood and contrast media before injection may increase the risk of thromboembolism and should therefore be avoided.

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**17.01.02 FOR USE IN BODY CAVITIES**

**IODINATED IONIC CONTRAST MEDIA**

**Indications**
They are used mainly for urography and angiography.

**Specific consideration**
They should be administered with great caution to patients with asthma or a history of allergy and should be avoided in patients with known hypersensitivity to contrast media or to iodine. Caution is needed in patients with severe hepatic or renal impairment or others who may be at increased risk of renal failure. Dehydrated patients should have their fluids and electrolyte balance corrected before contrast media administration. Patient with multiple myeloma may be at particular risk if dehydrated, since precipitations of proteins in the renal tubules may lead to anuria and fatal renal failure. An increased risk of adverse effects has also been reported in patients with severe hypertension, advanced cardiac disease, phaeochromocytoma, sickle cell disease, or hyperthyroidism. Debilitated, severely ill, very old or very young patients are also at risk. All intravascular administration requires cautions in patients with occlusive vascular disorders. These media should not be given for hysterosalpinography in the presence of infection or inflammation of the pelvic cavity, nor during menstruation or in the pregnancy, (all abdominal radiography should be avoided in any case during pregnancy because of the risk of radiation to the fetus). The administration of iodine containing contrast media may interfere with thyroid function tests. There may also be interference with blood coagulation tests and certain urine tests.

**Adverse effects**
Many of the side effects of iodinated ionic contrast media can be attributed to the high osmolality which is a feature of these agents; reducing the osmolality through altering the ionic or molecular profile produces a reduced incidence of adverse effects. Most reactions occur within 5 to 10 minutes of injection, but they may be delayed. Common: nausea, metallic taste, vomiting, flushing and sensations of heat, weakness, dizziness, headache, coughing, rhinitis, sweating, sneezing, alchrymation, visual disturbances, pruritus, salivary gland enlargement, pallor, tachycardia, bradycardia, transient ECG abnormalities, haemodynamic disturbances, and hypotension. Infrequent: anaphylactoid or hypersensitivity reaction, pain at the site of injection, fibrinolysis and a possible depressant effect on blood coagulation factor, hyperthyroidism, renal toxicity. Rare: convulsions, paralysis, coma, rigors, ventricular fibrillation, pulmonary oedema, circulatory failure, and cardiac arrhythmia occurred.

**Dosage**
Route and dosage depend on procedure and preparation used (consult manufacturer’s literature).

**Products**

**IODINATED IONIC CONTRAST MEDIA 140-180 MG IODINE / ML  200 - 250 ML BOTTLE (DIFFERENT COMPANIES)**

**IODINATED NON-IONIC CONTRAST MEDIA 140-180 MG IODINE / ML  200 - 250 ML BOTTLE (DIFFERENT COMPANIES)**
GADOLINIUM AGENT CONTRAST MEDIA

Adverse Effects and Precautions

There may be headache, nausea, vomiting, and transient sensations of heat or cold or taste disturbances following injection of gadodiamide. Rarely, convulsions, hypotension, allergic or anaphylactoid reactions, and shock may occur. Paraesthesias, dizziness, and localised pain have also been reported. Transient elevations of serum iron and bilirubin values have been observed. There has been a report of acute pancreatitis developing in a patient shortly after injection of gadodiamide for hepatic imaging.

Interference with diagnostic tests.

Gadodiamide may interfere with colorimetric methods for measuring serum calcium concentrations, and severe pseudohypocalcaemia has been reported following the use of gadodiamide.

Pharmacokinetics

Gadodiamide is rapidly distributed into extracellular fluid. About 96% of a dose is excreted unchanged in the urine within 24 hours. An elimination half-life of about 70 minutes has been reported. Gadodiamide is not bound to plasma proteins.

Uses and Administration

Gadodiamide is a nonionic paramagnetic agent used for contrast enhancement in magnetic resonance imaging of cranial and spinal structures and of the whole body, and in angiography.

Gadodiamide is available as a solution containing 287 mg/mL (0.5 mmol/mL). The usual dose in adults is 0.2 mL/kg (0.1 mmol/kg) intravenously. The dose may be increased to up to 0.6 mL/kg (0.3 mmol/kg) for whole body imaging and for angiography, but doses of greater than 60 mL are not usually required.

Products

IODINATED NON-IONIC ISO OSMOLALITY CONTRAST MEDIA

Products

IODINATED NON-IONIC ISO OSMOLALITY CONTRAST MEDIA 300-350 MG IODINE / ML 50 - 200 ML BOTTLE
IODINATED NON-IONIC ISO OSMOLALITY CONTRAST MEDIA 350-400 MG IODINE / ML 50 - 200 ML BOTTLE
IODINATED NON-IONIC LOW OSMOLALITY CONTRAST MEDIA 300-320 MG IODINE / ML 50 - 200 ML BOTTLE
IODINATED NON-IONIC LOW OSMOLALITY CONTRAST MEDIA 350-370 MG IODINE / ML 50 - 200 ML BOTTLE

17.01.03 FOR USE IN ORAL GASTROENTEROGRAPHY

BARIUM SULFATE POWDER FOR ORAL SUSPENSION

Adverse Effects

Because barium sulfate is almost insoluble it lacks the severe toxicity characteristic of the barium ion; deaths have occurred following the administration of the more soluble barium sulfide in error for the sulfate. Constipation may occur after oral or rectal barium sulfate; impaction, obstruction, and appendicitis have occurred. Surgical removal of faecaliths has sometimes been necessary. Cramping or diarrhoea have also been reported. Venous intravasation has led to the formation of emboli; deaths have occurred. Perforation of the bowel has led to peritonitis, adhesions, granulomas, and a high mortality rate. ECG abnormalities have occurred during the use of barium sulfate enemas. Accidental aspiration into the lungs has led to pneumonitis or granuloma formation.

Hypersensitivity.

A survey of hypersensitivity reactions to barium preparations found that although barium is inert many of the additives used in formulation have the potential to cause reactions. Of 106 reactions reported or found in the literature, 61% involved the skin and only 8% the respiratory tract; unconsciousness was reported in 8% of cases. In
view of the frequency of use of barium preparations, such adverse reactions must be very rare, but radiologists should be aware that they may be somewhat more common than is usually appreciated. A number of severe reactions associated with the use of barium enemas supplied with an inflatable latex cuff may have been due to leaching of components from the latex.

**Precautions**

Barium sulfate should not be given to patients with intestinal obstruction and care is needed in those with conditions such as pyloric stenosis or lesions that may predispose to obstruction. Adequate hydration should be ensured after the procedure to prevent severe constipation.

It is contra-indicated in patients with gastrointestinal perforation, and should be avoided, particularly when given rectally, in those at risk of perforation, such as patients with acute ulcerative colitis or diverticulitis and following rectal or colonic biopsy, sigmoidoscopy, or radiotherapy.

**Uses and Administration**

Barium sulfate is used as a contrast medium for X-ray examination of the gastrointestinal tract involving single- or double-contrast techniques or computed tomography.

The dose of barium sulfate is dependent upon the type of examination and technique employed. For examination of the oesophagus, up to 150 mL of a 50 to 200% w/v suspension may be given by mouth. For examination of the stomach and duodenum, up to 300 mL of a 30 to 200% w/v suspension may be given by mouth. For examination of the small intestine, 100 to 300 mL of a 30 to 150% w/v suspension may be given by mouth. For examination of the colon, 200 mL to 2 litres of a 20 to 130% w/v suspension may be given as an enema.

For double-contrast examination, gas can be introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide; separate gas-producing preparations based on sodium bicarbonate are also available. Air administered via a tube may be used as an alternative to carbon dioxide.

**Intussusception.**

Contrast media enemas and ultrasound are both used in the diagnosis of intussusception, a condition in infants where part of the intestine prolapses into the lumen of an adjacent part causing an obstruction. However, some consider ultrasound to be superior for diagnosis and reserve enemas for the therapeutic reduction of intussusception.

Reduction is achieved as a result of the hydrostatic pressure of the enema pushing the intestine back into its natural position. Although there is extensive experience using barium enemas for reduction some centres prefer to use water-soluble contrast media so as to minimise the risk of chemical peritonitis if perforation of the bowel occurs. Other agents used instead of barium for reduction include air enemas or ultrasound guided saline enemas, both of which avoid or reduce radiographic exposure. Surgery is indicated when enema therapy fails or is considered unsuitable.

**Products**

BARIUM SULFATE POWDER FOR ORAL SUSPENSION 4.5-5 % W / W, FOR USE IN COMPUTED TOMOGRAPHY 225-260 ML BOTTLE

BARIUM SULFATE POWDER FOR ORAL SUSPENTION 95-105 % W / W, POWDER WIEGHT 330-360 GM

IODINATED IONIC CONTRAST MEDIA

Products

IODINATED IONIC CONTRAST MEDIA 300-370 MG IODINE / ML 100 ML BOTTLE

IODINATED NON-IONIC CONTRAST MEDIA 300-370 MG IODINE / ML 100 ML BOTTLE

17.01.04 FOR USE IN RECTAL GASTROENTEROGRAPHY

BARIUM SULFATE POWDER FOR RECTAL SUSPENTION

See Barium sulfate powder for oral suspension

Products

BARIUM SULFATE POWDER FOR RECTAL SUSPENTION 95-105 % W / W, WITH DISPOSABLE ENEMA APPLICATION KIT INCLDING TUBING AND RECTAL ENEMA TIP, POWDER WEIGHT 390-420 GM
ADRENALINE® · 109, 134
ADRIBLASTINA® · 451
ADRIM® · 451
ADVANTAN® · 583
ADVAQUEENIL® · 531
ADVIL® · 522
AEROBEC FORTE® · 143
AEROBEC® · 143
AEROLIN® · 137
AGGARSTAT® · 118
AGIOLAX® · 46
AKAMON® · 161
AKINETON® · 228
AKNE-MYCIN® · 591
AL RAZI CALAMIN® · 614
ALARIN® · 150
ALBENDAZOLE · 321
ALBUMIN · 507
ALBUMIN KABI® · 508
ALCOHOL DEPENDENCE · 234
ALDACTONE® · 62
ALDESLEUKIN · 442
ALDORAM® · 62
ALEMTUZUMAB · 480
ALENDOMAX® · 360
ALENDRONIC ACID · 359
ALERGOFTALV® · 552
ALEXAN® · 461
ALFACALCIDOL · 514
ALFACORT® · 582
ALFENTANYL · 643
ALKERAN® · 447
ALKYLATING DRUGS · 443
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Acne · 588
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ADRENALINE · 108, 133

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