Student Formulary - Version 2016

Compiled for medical and pharmacy students years 1-5 and 1-4 respectively

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Foreword: This formulary provides brief clinical pharmacology and therapeutics notes on the most commonly prescribed drugs in primary and secondary care here in Northern Ireland. It is an educational resource for Queen’s undergraduate medical and pharmacy students and should NOT be used in clinical practice for prescribing. Students should use the hyperlinks in the contents and alphabetical list pages to navigate to the page of interest and the return hyperlinks throughout the document to return back to the relevant listing pages.

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**Gastro-intestinal system**

**Ranitidine**

**Drug Class:** Histamine H\(_2\) receptor antagonists

**Other commonly used drugs in this class:** Cimetidine, Famotidine, Nizatidine

**Mode of Action**

*Target:* Histamine H\(_2\) receptor in gastric parietal cell

*Action:* Competitive antagonist

*Effect:* Prevent binding of histamine to its H\(_2\) receptor on the gastric parietal cell reducing stimulation of gastric acid secretion

*Overall effect:* Reduce gastric acid secretion

**Clinical indications:**

GORD; Peptic Ulcer Disease; Dyspepsia

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Prescribing and Safety

Ranitidine – 150mg BD or 300mg nocte for up to 12 weeks depending on indication
Reduce in hepatic or renal impairment

Adverse effects:

Common:
- Diarrhoea, Headache, Dizziness

Less Common:
Rash, confusion, depression, blood disorders

Important:
- Gynaecomastia, impotence (cimetidine only)

Contra-indications and cautions
- Caution in hepatic or renal impairment
- Avoid in pregnancy
- \( H_2 \) receptor antagonists may mask the symptoms of gastric cancer – in patients presenting with ‘alarm features’ (bleeding, dysphagia, recurrent vomiting, weight loss) it is important to rule out malignancy before commencing therapy

Interactions
- Cimetidine is a cytochrome P450 inhibitor. Avoid concomitant use of cimetidine in patients stabilised on warfarin, theophylline and phenytoin.
- Ranitidine, famotidine and nizatidine do not share the drug metabolism inhibitory properties of cimetidine.

Therapeutic drug monitoring

Safety:

Efficacy: Improvement/resolution of symptoms

Patient communication:
Advise patients to re-consult if symptoms do not improve or they develop any ‘alarm features’: bleeding, dysphagia, recurrent vomiting, weight loss.

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Omeprazole

**Drug Class:** Proton pump inhibitor (PPI)

**Other commonly used drugs in this class:** Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole

**Mode of Action**

![Diagram of Gastric Parietal Cell]

**Target:** \( \text{H}^+ \text{K}^+ \text{ATPase} \) pump at the secretory surface of gastric parietal cells

**Action:** Irreversible inhibitor

**Effect:** Inhibits final transport of hydrogen ions into gastric lumen; thereby inhibiting gastric acid secretion

**Overall effect:** Reduces gastric acidity

**Clinical indications:**

- Treatment of gastric and duodenal ulcers (peptic ulcer disease)
- Prevention and treatment of NSAID-associated ulcers
- Helicobacter pylori eradication (in combination with two antibiotics - Triple Therapy)
- Reflux oesophagitis/Gastro-oesophageal reflux disease (GORD)
- Zollinger-Ellison syndrome

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Prescribing and Safety

Omeprazole 20-40mg daily (60-120mg daily in Zollinger-Ellison syndrome)
Reduce dose in hepatic impairment
Prescribe PPIs at lowest effective dose, for the shortest time period; need for long term treatment should be reviewed periodically. E.g. patients started on high dose therapy with any PPI should be followed up in 8 weeks

Adverse effects

Common:
- GI disturbance e.g. nausea, vomiting, abdominal pain, flatulence, diarrhoea, constipation, Headache

Important:
- Rebound acid hypersecretion, Hepatitis, Interstitial nephritis, Blood disorders – leucopenia, leucocytosis, pancytopenia, thrombocytopenia, Increased risk of Clostridium difficile infection, hypomagnesaemia

Contra-indications and cautions

PPIs may mask symptoms of gastric cancer – in patients presenting with ‘alarm features’ (bleeding, dysphagia, recurrent vomiting, weight loss) it is important to rule out malignancy before commencing PPI therapy.

Avoid in pregnancy and breast-feeding.

Interactions

Slight variation between different PPIs

- Warfarin (Omeprazole and esomeprazole increase anticoagulant effect)
- Clopidogrel (Omeprazole and esomeprazole may reduce antiplatelet effect)

Therapeutic drug monitoring

Safety: Consider monitoring serum magnesium levels before and during prolonged treatment especially if taking other drugs that lower Mg e.g. diuretics or if taking digoxin.

Efficacy: Improvement/resolution of symptoms e.g. heartburn

Patient communication:
Advise patients to re-consult if symptoms do not improve or they develop any ‘alarm features’: bleeding, dysphagia, recurrent vomiting, weight loss. Avoid foods and drinks that make symptoms worse, avoid large or late meals and avoid lying down immediately after meal.

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**Loperamide**

**Drug Class:** Antimotility drugs

**Mode of Action**

**Target:** Opioid mu receptors in the myenteric plexus of the large intestine

**Action:** Agonist

**Effect:** Reduced tone in the circular and longitudinal muscles of the intestinal wall, inhibition of peristalsis

**Overall effect:** Slows intestinal motility

**Clinical indications:**

- Adjunct to rehydration in acute diarrhoea in adults and children over 4 years; Chronic diarrhoea (in adults only)

**Prescribing and Safety**

Acute diarrhoea: 4mg initially followed by 2mg after each loose stool for up to 5 days, usual doae 6-8mg daily

Chronic diarrhoea in adults: 4-8mg daily in divided doses

**Adverse effects**

**Common:**

- Abdominal cramps, dizziness, flatulence, headache, nausea

**Important:**

- Paralytic ileus

**Contra-indications and cautions**

- Avoid in active ulcerative colitis, antibiotic-associated colitis, infective colitis or other conditions where inhibition of peristalsis should be avoided
- Discontinue if abdominal distension develops

**Therapeutic drug monitoring**

**Efficacy:** Improvement/resolution of diarrhoea

**Patient communication:**

This medication should not be given to children under the age of 4 years. Maintain adequate fluid intake.

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**Mesalazine (5-aminosalicylic acid)**

**Drug Class:** Aminosalicylates

**Other commonly used drugs in this class:** Olsalazine, Sulfasalazine, Balsalazide

**Mode of Action:** Not fully understood but thought to be as follows:

**Target:** Cyclooxygenase enzymes in the colon

**Action:** Inhibitor

**Effect:** Inhibit mucosal production of arachidonic acid metabolites such as prostaglandins

**Overall effect:** Reduced colonic inflammation

**Clinical indications:**

Rheumatoid arthritis; Induction and maintenance of remission of ulcerative colitis; Treatment of Crohn’s disease

**Prescribing and Safety**

Rheumatology – 500mg/day increasing by 500mg weekly to 2g-3g/day.

Gastroenterology – 1g-2g orally four times a day until remission occurs, reducing to a maintenance dose of 500mg four times a day.

Available as oral tablet, enemas and suppositories

**Adverse effects:**

**Common:**

GI upset (diarrhoea, nausea, vomiting, abdominal pain)

**Important:**

Acute pancreatitis; Blood disorders including agranulocytosis; Lupus erythematosus-like syndrome (sulfasalazine); Renal dysfunction – interstitial nephritis, nephrotic syndrome not to be used in moderate or severe renal impairment.
Contra-indications and cautions

- Caution in the elderly, pregnancy and breastfeeding, patients with a history of asthma and those with hepatic or renal impairment (avoid if severe)
- Caution with SULFASALAZINE in patients with G6PD deficiency – observe closely for signs of haemolytic anaemia
- Avoid in patients with known salicylate or sulphonamide hypersensitivity
- Stop aminosalicylate if it is suspected that the patient has developed a blood dyscrasia

Interactions

- Lactulose – co-prescription will reduce 5-ASA efficacy
- Azathioprine (increased risk of leucopenia)
- Mercaptopurine (increased risk of leucopenia)
- Digoxin – absorption of digoxin may be reduced, review dosage requirement after introduction of aminosalicylate

Therapeutic drug monitoring

Safety: Baseline FBC, LFTs, ESR, CRP should be checked monthly for the first 3 months then 3 monthly thereafter. Re-check blood count immediately if blood dyscrasia suspected. Also check renal function (U+E) before starting an oral aminosalicylate, at 3 months of treatment and annually thereafter (more frequently in renal impairment).

Patients should be asked about oral ulceration/sore throat, unexplained rash or unusual bruising at every consultation.

Efficacy: Improvement/resolution of symptoms

Patient communication:
Advise patients receiving aminosalicylates to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment.

Sulfasalazine may cause yellow-orange discoloration of skin, urine and other body fluids; some soft contact lenses may be stained.

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Laxatives

**Mechanism of action of laxatives**

**Bulk-forming laxatives** e.g. Ispaghula Husk are polysaccharide polymers which are not broken down in the upper GI tract. They increase stool volume, forming a bulky mass in the bowel lumen. This activates the stretch reflex which stimulates peristalsis.

**Osmotic laxatives** e.g. Lactulose, Macrogol are poorly absorbed solutes which are not absorbed from the gut and hence produce an osmotic gradient within the bowel. Water is drawn out of cells and into the bowel lumen, accelerating the transfer of gut contents through the small intestine. This leads to an abnormally large volume entering the large intestine and distension and purgation occur within about an hour.

The main action of **stimulant laxatives** e.g. Senna is to increase electrolyte and water secretion by the GI mucosa and to increase peristalsis. This improves transit through the gut. Senna is an anthroquinone stimulant laxative which directly stimulates the myenteric plexus leading to increased peristalsis and defecation.

**Clinical indications:**

- Constipation; Hepatic encephalopathy (lactulose)

**Prescribing and Safety**

Ispaghula Husk as Fybogel – 1 sachet twice daily after meals
Lactulose – 15ml twice daily in constipation, 30-50ml 3 times daily in hepatic encephalopathy

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Macrogol – 1-2 sachets daily
Senna – 2-4 tablets nocte

Adverse effects:

Common:
- Abdominal distension and cramps; Flatulence; Diarrhoea

Important:
- Electrolyte disturbances

Contra-indications and cautions
- Caution with lactulose in patients who are lactose intolerant
- Avoid in intestinal obstruction or perforation, severe inflammatory bowel disease and severe dehydration
- Discontinue if patient develops symptoms of fluid or electrolyte disturbance

Interactions

- Therapeutic drug monitoring

Safety:

Efficacy: Improvement/resolution of symptoms

Patient communication:
Explain to patients that they should drink plenty of fluids while taking laxatives to avoid dehydration and/or bowel obstruction. Patients should also maintain a healthy diet that includes fiber, fruit and vegetables.

Additional information:
Before prescribing a laxative it is important to rule out bowel cancer as a cause of constipation.

Osmotic and bulk-forming laxatives take 2-3 days to reach their full effect.

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**Cardiovascular system**

**Digoxin**

**Drug Class:** Cardiac glycosides

**Other commonly used drugs in this class:** None

**Mode of Action**

![Diagram of sodium-potassium pump and calcium exchange](image)

**Target:** Na⁺/K⁺ ATPase membrane pump

**Action:** Inhibitor

**Effect:** Increase in intracellular sodium. This leads to a subsequent rise in intracellular calcium through the Na⁺/Ca²⁺ exchanger on cardiac myocytes. Phases 4 and 0 of the cardiac action potential are prolonged leading to an increase in end diastolic volume.

**Overall effect:** Positive inotropic effect (increased end diastolic volume leads to increased force of ventricular contraction according to Frank Starling curve), negative chronotropic effect – increases cardiac contractility, decreases heart rate

**Clinical indications:**

- Ventricular rate control in supraventricular arrhythmias, particularly persistent and permanent atrial fibrillation and atrial flutter
- Heart failure

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Prescribing and Safety
- 0.75–1.5mg in divided doses over 24 hours for rapid control of atrial fibrillation or flutter
- 125–250micrograms daily for maintenance of atrial fibrillation or flutter
- 62.5-125micrograms daily for heart failure (patient in sinus rhythm)
Reduce dose in the elderly and those with renal impairment

Adverse effects

DIGOXIN TOXICITY:

Confusion; Loss of appetite; Nausea, vomiting, diarrhoea; Evidence of cardiotoxicity – palpitations, arrhythmias, conduction disturbances; eosinophilia, rash, Blurred or yellow vision

If digoxin toxicity is known or strongly suspected and withdrawal of the drug/correction of electrolyte disturbances are ineffective, DIGOXIN-SPECIFIC ANTIBODY FRAGMENTS are indicated.

Contra-indications and cautions
- Caution in sick sinus syndrome, hypokalaemia, hypomagnesaemia, hypercalcaemia, thyroid disease, severe respiratory disease and in patients who have had a recent MI
- Avoid in heart block, Wolff-Parkinson-White syndrome, ventricular tachycardia or fibrillation, myocarditis and constirctive pericarditis
- Reduce dose in renal impairment

Interactions
- Amiodarone (increased plasma digoxin concentration – halve dose of digoxin)
- Calcium channel blockers (increased plasma digoxin concentration)
- Drugs which cause hypokalaemia e.g. diuretics increase the risk of cardiotoxicity (secondary to the hypokalaemia), proton pump inhibitors through hypomagnesaemia.

Therapeutic drug monitoring

DIGOXIN HAS A NARROW THERAPEUTIC INDEX

Safety: Monitor plasma digoxin concentration regularly if toxicity suspected, monitor renal function and adjust dose in renal impairment

Efficacy: Depends on indication e.g. reduced ventricular rate

Patient communication

Patients should be made aware of the symptoms of toxicity (nausea, vomiting, visual disturbance, confusion or dizziness) and advised to present early if any of these become apparent.
**Bendroflumethiazide**

**Drug Class:** Thiazide diuretic

**Other commonly used drugs in this class:** Hydrochlorothiazide, Indapamide (Thiazide-like diuretic), Chlortalidone (Thiazide-like diuretic), metolazone (Thiazide-like diuretic)

**Mode of Action**

**Target:** $\text{Na}^+\text{Cl}^-$ symporter in distal convoluted tubule

**Action:** Inhibitor

**Effect:** Inhibits sodium and chloride reabsorption in the cortical diluting segment of the distal convoluted tubule

**Overall effect:** Natriuresis and reduction in blood volume and pressure

**Clinical indications:**

- Hypertension – alone in mild hypertension, combined with other drugs in severe hypertension (Has been superceded by indapamide in NICE 2011 hypertension guidance)
- Oedema in mild to moderate heart failure (usually use loop diuretic in heart failure)
Prescribing and Safety

Bendroflumethiazide: 5-10mg mane for management of oedema; 2.5mg mane for hypertension

Indapamide 2.5mg mane for hypertension

Adverse effects

Common:

- Altered plasma-lipid concentrations (elevated LDL cholesterol), gout, electrolyte disturbances – hypokalaemia, hyponatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, postural hypotension
- Metabolic disturbances – hyperglycaemia, hyperuricaemia (gout)

Important:

- Impotence, blood disorders

Contra-indications and cautions

- Caution in malnutrition, renal impairment and in patients with a history of gout or diabetes
- Avoid in Addison’s disease, symptomatic hyperuricaemia and in refractory hyponatraemia, hypokalaemia or hypercalcaemia

Interactions

- Other antihypertensives (increased hypotensive effect)
- Antidiabetic drugs (reduced hypoglycaemic effect)
- Lithium (increased plasma lithium concentration, risk of toxicity)
- NSAIDs (impaired diuresis AND increased risk of nephrotoxicity)
- Other drugs causing hyponatraemia (diuretics, antidepressants, carbamazepine)

Therapeutic drug monitoring

Safety: Monitor electrolytes (U+E) to detect adverse effects, particularly if giving a high dose or if patient has pre-existing renal impairment

Efficacy: Depends on indication e.g. reduction in blood pressure, reduction in oedema

Additional comments

Thiazide diuretics should not be used to treat gestational hypertension. They are ineffectual if eGFR <30mLs/min (except metolazone)
**Furosemide**

**Drug Class:** Loop diuretic

**Other commonly used drugs in this class:** Bumetanide, torsemide

**Mode of Action**

**Target:** Na\(^+\) K\(^+\) 2Cl\(^-\) symporter in the thick ascending limb of the loop of Henlé

**Action:** Competitive inhibitor at the chloride binding site on the symporter

**Effect:** Prevents the transport of sodium from the lumen of the loop of Henle into the basolateral interstitium. Consequently, the lumen becomes more hypertonic while the interstitium becomes less hypertonic, which in turn diminishes the osmotic gradient for water reabsorption throughout the nephron

**Overall effect:** Diuresis – increased urine output

**Clinical indications:**

- Pulmonary oedema due to LV failure; Chronic heart failure; Resistant hypertension

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Prescribing and Safety

Furosemide: 20-40mg mane for management of oedema (resistant oedema – 80-120mg daily); 40-80mg daily for resistant hypertension

Bumetanide: 1mg mane, repeated after 6-8 hours if necessary

Adverse effects

Common:
- GI disturbance; Postural hypotension
- Electrolyte disturbances – hyponatraemia, hypokalaemia, hypocalcaemia

Important:
- Metabolic disturbances – hyperglycaemia, hyperuricaemia (gout)
- Ototoxicity; Nephrotoxicity; Hepatic encephalopathy

Contra-indications and cautions
- Caution in hypovolaemia, hypotension, prostatic hypertrophy and in patients with history of diabetes or gout
- Avoid in anuria, severe hyponatraemia/hypokalaemia and in comatose or precomatose states associated with liver cirrhosis; renal failure (nephrotoxic), severe hypokalaemia/hyponatraemia

Interactions
- Antihypertensives (increased hypotensive effect)
- NSAIDs (impaired diuresis AND increased risk of nephrotoxicity)
- Aminoglycoside antibiotics and vancomycin (increased risk of ototoxicity)
- Lithium (increased plasma lithium concentration, risk of toxicity)
- Thiazide diuretics (increased risk of electrolyte disturbance)
- Digoxin (risk of cardiotoxicity)

Therapeutic drug monitoring

Safety: Electrolytes (U+E) should be checked at baseline and monitored during treatment to detect adverse effects

Efficacy: Depends on indication e.g. reduction in pulmonary oedema and associated dyspnoea, reduction in blood pressure

Additional comments

Establish adequate urine output before giving a loop diuretic. Patients with renal impairment and low eGFR may not respond to normal doses of loop diuretics due to poor perfusion of the target tissues – higher doses may be required.

Do not use loop diuretics in the management of gestational hypertension, not for dependent ankle oedema only i.e. no clinical signs of heart failure nor as first-line monotherapy for hypertension.
Spironolactone

Drug Class: Aldosterone-dependent potassium sparing diuretics

Other commonly used drugs in this class: Eplerenone

Mode of Action

Target: Intracellular aldosterone receptors (mineralocorticoid receptors (MR)) in the renal tubules

Action: Competitive antagonist, blocks aldosterone-MR translocation into the nucleus reducing the production of aldosterone induced proteins (AIPs)

Effect: Inhibits Na⁺/K⁺ exchange in the distal tubule and collecting ducts, promoting potassium retention and sodium and water loss

Overall effect: Weak diuresis, potassium retention and hypotensive effect

Clinical indications:

- Oedema in congestive heart failure – shown to improve survival
- Ascites
- Primary hyperaldosteronism
- Nephrotic syndrome
Prescribing and Safety

Spironolactone: Ascites: 50mg twice daily (increase to 200mg twice daily if required)
   Heart failue 25mg once daily

Adverse effects:
Common:
   • GI upset, Hyperkalaemia (less commonly hyponatraemia and hyperuricaemia)

Important:
   • Gynaecomastia/hypogonadism, impotence in males, menstrual irregularities in females (due to cross-reaction with intracellular androgen receptors), loss of libido
   • Acute renal failure

Contra-indications and cautions
   • Caution in the elderly and those with renal impairment (avoid if severe)
   • Avoid in hyperkalaemia, hyponatraemia, anuria and Addison’s disease

Interactions
   • Drug affecting RAAS (increased risk of hyperkalaemia) – ACE inhibitors, ARBs, direct renin inhibitors
   • Other potassium sparing diuretics e.g. amiloride, triamterene (increased risk of hyperkalaemia)
   • Potassium supplements
   • Antihypertensives (increased hypotensive effect)
   • NSAIDs (increased risk of nephrotoxicity)
   • Lithium – excretion is inhibited by spironolactone

Therapeutic drug monitoring

Safety: Perform baseline U&E and LFT. Re-check U&E after 1 week then every 4 weeks for the first 12 weeks and 3 monthly thereafter for a year then 6 monthly for the duration of therapy.

Efficacy: Depends on indication – reduced fluid retention, daily weight, improvement in symptoms of heart failure, etc.

Patient communication:
Patients should be advised to take this medication with or after food.

Explain to patients that if they experience excessive vomiting or diarrhoea (risk of dehydration), they should withhold the spironolactone immediately and contact their GP.

Patients should be advised to avoid salt substitutes such as LO-SALT which are high in potassium.

Explain to patients that they should not take any NSAID unless prescribed by their doctor – avoid buying ibuprofen etc. over the counter.

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Amiodarone

Drug Class: Class III anti-arrhythmics

Other commonly used drugs in this class: dronaderone

Mode of Action: complex/unclear

Target: non-selective for Na channel, Ca channel and α-adrenoceptors

Action: Non-selective inhibitor of the above channels and receptor

Effect: prolongs the cardiac action potential seen as an increase in the QT interval on the ECG

Overall effect: Class III antiarrhythmic effect

Clinical indications:

Amiodarone is used in the treatment of a range of cardiac dysrhythmias, including:

- Rhythm control in atrial fibrillation
- Atrial flutter
- Ventricular tachycardia and fibrillation
- Tachyarrhythmias associated with Wolff-Parkinson-White syndrome

Prescribing and Safety

Starting dose – 200mg 3 times daily for 1 week then twice daily for the following week

Maintenance dose – 200mg once daily

Adverse effects

Common:

- Bradycardia, hyper/hypo-thyroidism, jaundice, nausea, slate-grey skin discolouration, phototoxicity, Pulmonary fibrosis, Hepatotoxicity, reversible corneal microdeposits, sleep disorders, taste disturbances, tremor and vomiting

Important:

- Peripheral neuropathy, myopathy
- Optic neuritis/neuropathy (can lead to blindness)

Contra-indications and cautions

- Caution in heart failure and the elderly
- Avoid in sinus bradycardia, sino-atrial heart block, thyroid dysfunction and iodine sensitivity
Avoid intravenous amiodarone in severe respiratory failure, circulatory collapse and severe arterial hypotension
Discontinue if patient develops optic neuritis/neuropathy

Interactions
- Other anti-arrhythmics (increased myocardial depression)
- Digoxin (amiodarone increases plasma digoxin concentration – halve digoxin dose)
- Warfarin (increased anticoagulant effect)
- Beta blockers, calcium channel blockers (increased risk of bradycardia, AV block and myocardial depression)
- Simvastatin (increased risk of myopathy)
- Tricyclic antidepressants (increased risk of ventricular arrhythmias)
- Phenytoin (increased plasma phenytoin concentration)
- Lithium (increased risk of ventricular arrhythmias)

Therapeutic drug monitoring
Safety: LFTs and TFTs should be performed before starting treatment and re-checked every 6 months. Serum potassium levels checked before treatment. Those receiving amiodarone intravenously should have ECG monitoring and resuscitation facilities available and have liver transaminases closely monitored. Patients should also have a chest x-ray before starting amiodarone.

Also monitor patients clinically for adverse effects.

Efficacy: Restoration of normal sinus rhythm

Patient communication:
Where possible, patients should avoid exposure to direct sunlight and sun lamps during treatment and for several months after coming off amiodarone. Advise patients to wear high factor sunscreen while on this medication.

Advise patients that this medication can produce changes in their eyes which may cause them to be dazzled by car headlights when driving at night.

Additional information:
If a patient requires repeated or continuous infusion of amiodarone a central venous catheter is recommended as peripheral infusion may cause pain and inflammation. In addition, ECG monitoring and resuscitation facilities must be available during IV use. Infusions should ONLY be diluted in 5% dextrose NOT 0.9% saline.
**Bisoprolol**  
**Drug Class:** Beta blockers

**Other commonly used drugs in this class:** Cardioselective ($\beta_1$ only) – Atenolol, Metoprolol, Nebivolol  
Non-cardioselective ($\beta_1$ and $\beta_2$) – Carvedilol, Propranolol

**Mode of Action**

![Image of Mode of Action Diagram]

**Target:** Beta adrenoceptors (therapeutic effects through $\beta_1$ receptors)  

**Action:** Competitive antagonist

**Effect:** Inhibits binding of normal ligand noradrenaline released from sympathetic adrenergic neurones. This inhibits activation of adenylyl cyclase enzymes leading to reduced cyclic AMP. This in turn leads to reduced intracellular calcium levels.

**Overall effect:** Reduce contractility (negative intropy), reduce heart rate (negative chronotropy), reduce blood pressure, reduce cardiac work

NB. Effects of these drugs depend on the degree of sympathetic activity of the patient and are slight in subjects at rest.

**Clinical indications:**

- Angina pectoris
- Myocardial infarction
- Heart failure
- Resistant hypertension (step 4 in the NICE 2011 guidelines for hypertension)
- Hyperthyroidism (propanolol can be used to control symptoms before definitive treatment begins to take effect)
- Other uses: used to alleviate symptoms of anxiety, prophylaxis of migraine.

**Prescribing and Safety**

Bisoprolol – 5-10mg once daily (max. 20mg)
(In heart failure – start at 1.25mg once daily and gradually increase if tolerated)

**Adverse effects:**

**Common:**
- Dizziness, fatigue, cold hands, impotence, headache

**Important:**
- Hypotension
- Bronchoconstriction – important in asthma, COPD
- Bradycardia and heart block
- Hypoglycaemia – in diabetic patients, beta blockers may mask ‘hypo’ warning signs
- Peripheral vasoconstriction including exacerbation of intermittent claudication and Raynaud’s phenomenon

**Contra-indications and cautions**
- Caution in heart failure, peripheral vascular disease (avoid if severe), COPD, diabetes mellitus (avoid if poorly controlled) and portal hypertension
- Avoid in asthma, heart block and hypotension

**Interactions**
- Alcohol (increased hypotensive effect)
- Other antihypertensives (increased hypotensive effect)
- Anti-arrhythmics (bradycardia, myocardial depression, ventricular arrhythmias)
- Clonidine (increased risk of rebound hypertension when stopping beta blockers)

**Therapeutic drug monitoring**

**Safety:** When starting a beta blocker in heart failure, monitor patient closely to ensure no exacerbation of condition. If COPD monitor lung function while on beta blocker.

**Efficacy:** Depends on indication – reduced frequency of angina attacks, reduction in blood pressure, improvement in symptoms of heart failure, control of hyperthyroid symptoms (propanolol)

**Patient communication:**

Explain to patients that they should not stop taking this medication unless told to do so by their doctor.
**Doxazosin**

**Drug Class:** α1 specific Alpha blockers

**Other commonly used drugs in this class:** Alfuzosin, Indoramin, Prazosin, Tamulosin, Terazosin

**Mode of Action**

![Diagram of drug action](image)

**Target:** Alpha adrenoceptor

**Action:** Antagonist

Effect: Inhibits binding of normal ligand noradrenaline released from sympathetic adrenergic neurones. This inhibits activation of phospholipase-C enzyme leading to reduced inositol triphosphate; this in turn blocks the downstream phosphorylation cascade.

**Overall effect:** Vascular smooth muscle relaxation, vasodilatation and reduction in arterial blood pressure

**Clinical indications:**

- Hypertension
- Benign prostatic hyperplasia (α1 specific)
- Raynaud’s syndrome (prazosin)
Prescribing and Safety
Doxazosin: starting dose 1mg once daily; maintenance dose 4-16mg once daily
Indoramin: starting dose 25mg twice daily; maintenance dose 50-200mg daily in 2-3 divided doses
Prazosin: starting dose 500 micrograms 2-3 times daily; maximum 20mg daily in divided doses
Terazosin: starting dose 1mg nocte; maintenance dose 2-10mg once daily

Adverse effects

Common:
- Anxiety; back pain; coughing; dyspnoea; fatigue; influenza-like symptoms; myalgia; paraesthesia; sleep disturbance; vertigo

Important:
- Postural hypotension

Contra-indications and cautions
- Caution in the elderly, Parkinson’s disease and those undergoing cataract surgery (risk of intra-operative floppy iris syndrome)
- Use with caution when giving first dose as may cause hypotension and collapse – give first dose at bedtime
- Avoid in patients with a history of postural hypotension or micturition syncope

Interactions
- Other antihypertensives (increased hypotensive effect)
- MAOIs (enhanced hypotensive effect)

Therapeutic drug monitoring

Safety:

Efficacy: Depends on indication e.g. reduction in blood pressure

Patient communication
Warn patients that this medication may affect their ability to perform skilled tasks e.g. driving.

Patients should take the first dose of their medicine at night on retiring to bed due to the risk of first dose hypotension.
**Rami**pril

**Drug Class:** Angiotensin Converting Enzyme (ACE) inhibitor

**Other commonly used drugs in this class:** Capto*pri*l, Enalap*ril*, Lisino*pri*l, Perindo*pri*l, Trandolap*ril*.

**Mode of Action**

**Target:** Angiotensin Converting Enzyme (ACE)

**Action:** Competitive inhibitor

**Effect:** Inhibits synthesis of potent vasoconstrictor peptide angiotensin II leading to vascular smooth muscle relaxation and vasodilatation

**Overall effect:** Reduced blood pressure

**Clinical indications:**

- Hypertension (1st line drug in younger caucasian patients <55 years)
- Heart failure and secondary prevention Post-MI
- Type I Diabetic nephropathy
- Following acute MI
Prescribing and Safety

Starting dose: Hypertension 2.5 mg daily / 1.25mg daily in heartfailure or elderly
Maintenance dose: 10mg daily

Adverse effects:
Common:
- Persistent dry cough, hyperkalaemia, increase in serum creatinine
- (First dose) hypotension – may be profound

Important:
- Acute renal failure, cholestatic jaundice/hepatitis
- Angioedema, hypersensitivity reactions

Contra-indications and cautions
- Caution in patients taking diuretics, renal impairment, severe aortic stenosis
- Avoid in patients with known hypersensitivity reaction to ACE inhibitors, in pregnancy and known or suspected renovascular disease
- Discontinue ACE inhibitors if patient develops jaundice or markedly elevated liver enzymes – risk of hepatic necrosis
- Do not prescribe to women of child bearing age if they are trying to conceive.

Interactions
- Diuretics (increased risk of hypotension)
- Potassium sparing diuretics (increased risk of hyperkalaemia) – amiloride, triamterene, spironolactone, eplerenone
- Potassium salts
- Avoid co-prescription with ARBs candesartan etc. or Direct renin inhibitors – aliskiren
- Lithium
- Immunosuppressants – ciclosporin (increased risk of hyperkalaemia)

Therapeutic drug monitoring

Safety: Urea and electrolytes (U+E), particularly looking at urea/creatinine and potassium levels for signs of hyperkalaemia or deterioration in renal function.

Efficacy: Depends on clinical indication but improvement in blood pressure, cardiac function or urinary albumin/creatinine ratio (UACR) for microalbuminuria.

Patient communication:
Explain the need for a blood test (U+E) before starting treatment and 1-2 weeks after treatment. If the patient develops a dry cough within the first few months then they should report this to their GP and their medication will be changed to an ARB. If the patient is at risk of first dose hypotension (e.g. elderly) then should take initial first dose at night.
Irbesartan

**Drug Class:** Angiotensin II Receptor Blocker (ARB)

**Other commonly used drugs in this class:** Candesartan, Losartan, Valsartan, Eprosartan, Olmesartan, Telmisartan.

**Mode of Action**

![Diagram of Angiotensin II receptor system]

**Target:** Angiotensin II AT$_1$ receptor

**Action:** Competitive antagonist

**Effect:** Selective inhibition of potent vasoconstrictor peptide angiotensin II leading to vascular smooth muscle relaxation and vasodilatation

**Overall effect:** Reduced blood pressure

**Clinical indications:**

- Hypertension
- Heart failure
- Post-MI
- Prevention of cardiovascular events in patients with established atherosclerotic cardiovascular disease and/or diabetes mellitus with target-organ damage
- Type II diabetic nephropathy
Prescribing and Safety

Irbesartan – 150mg once daily (elderly 75mg once daily)

Candesartan: Starting dose – 4mg once daily; Maintenance dose – 8-32mg

Losartan – 50mg once daily (12.5mg in heart failure, increase gradually if tolerated)

Use half the normal dose in renal impairment.

Adverse effects

Common:

- (First dose) hypotension – less marked than with ACE inhibitor, dizziness, hyperkalaemia, increase in serum creatinine

Important:

- Acute renal failure
- Angioedema (may be delayed onset)

Contra-indications and cautions

- Caution in aortic or mitral stenosis and in renal artery stenosis
- Avoid in pregnancy & breast-feeding; do not prescribe to women of child bearing age if they are trying to conceive.

Interactions

- Other antihypertensives (increased hypotensive effect)
- ACE inhibitors, Potassium sparing diuretics (increased risk of hyperkalaemia)
- Lithium

Therapeutic drug monitoring

Safety: Renal function should be checked at baseline via U+E – this should be repeated 1-2 weeks after starting treatment and annually thereafter. Older patients and patients with heart failure should also be closely monitored clinically.

Efficacy: Depends on indication e.g. reduction in blood pressure, improvement in symptoms of heart failure

Additional comments

ACE inhibitors are preferred in all settings except in type II diabetic nephropathy or where patient is unable to tolerate an ACE inhibitor due to persistent dry cough.

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**Glyceryl Trinitrate (GTN)**

**Drug Class:** Nitrates

**Other commonly used drugs in this class:** Isosorbide Mononitrate (ISMN), Isosorbide Dinitrate (ISDN)

**Mode of Action**

**Target:** Nitrate membrane receptor

**Action:** Nitrates are metabolised to form an NO group which stimulates guanylate cyclase enzymes to increase production of the second messenger cyclic GMP (cGMP)

**Effect:** Inhibits the entry of calcium ions into the cell leading to reduced intracellular calcium levels

**Overall effect:** Vascular smooth muscle relaxation and vasodilatation. Dilatation of the coronary arteries leads to improved myocardial oxygen supply while dilatation in the systemic venous system leads to reduced preload and oxygen demand.

GTN is a short acting preparation which exerts its effects within 1-2 minutes and works for up to an hour. ISMN and ISDN are longer acting preparations which take effect more slowly but last for up to 8 hours.

**Clinical indications:**

- Prophylaxis (ISMN, ISDN) and acute relief (GTN) of angina

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Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

GTN: 0.3-1mg sublingually as required
ISMN: 25-60mg daily (can be increased up to a maximum of 120mg daily if required)
ISDN: 30-120mg daily in divided doses

Adverse effects:
- Headache
- Postural hypotension
- Tachycardia
- Flushing
- Tolerance, particularly with long acting or transdermal nitrates – may be overcome by using ‘nitrate-free interval’ i.e. patient should be nitrate-free for 4-8 hours in every 24 hours

Contra-indications and cautions
- Caution in hypothyroidism, recent MI and heart failure
- Avoid in hypotension/hypovolaemia, aortic or mitral stenosis and cerebrovascular disease

Interactions
- Antihypertensives (increased hypotensive effect)
- Sildenafil, Tadalafil, Vardenafil (significantly increased hypotensive effect – avoid concomitant use)

Therapeutic drug monitoring
Safety: If giving nitrates IV it is necessary to monitor BP and heart rate

Efficacy: Resolution of angina symptoms during an acute attack (GTN), reduced frequency of angina attacks (ISMN, ISDN)

Patient communication:
Explain to patients how they should take their GTN – spray 1-2 times under the tongue and then close mouth. This medication is for use when the patient notices their angina symptoms – it is for relief of an acute attack.

Additional information:
Sulphhydryl (SH) groups are needed for nitrates to work effectively – tolerance arises as a result of depletion of these SH groups. Therefore, patients should have sufficient “nitrate free” periods. E.g. if taking Isosorbide Mononitrate MR tablets bd, dosing schedule should be 8 hours rather than 12 hours apart.
**Amlodipine**

**Drug Class:** Dihydropyridine calcium channel blockers

**Other commonly used drugs in this class:** Felodipine, Lercanidipine, Nifedipine

**Mode of Action**

![Diagram showing mode of action of Amlodipine](image)

**Target:** L-type calcium channels - Dihydropyridines favour depolarised closed Ca^{++} channels most commonly found in vascular smooth muscle cells

**Action:** Antagonist

**Effect:** Inhibit influx of calcium ions into vascular smooth muscle cells through L-type calcium channels

**Overall effect:** Decreased arterial smooth muscle contratility leading to vasodilatation

**Clinical indications:**

- Hypertension – first line treatment in patients aged> 55 years and/or Afro-Carribean
- Prophylaxis of angina
Prescribing and Safety

Starting dose – 5mg mane

Maintenance dose – 5-10mg once daily

Adverse effects

Common:

- Abdominal pain; dizziness; fatigue; flushing; headache; nausea; oedema; palpitation; sleep disturbances

Important:

- Heart failure in patients with poor left ventricular function

Contra-indications and cautions

- Caution in the elderly and those with heart failure (avoid if uncontrolled)

- Avoid in unstable angina, severe aortic stenosis and those who have had an MI in the last month

Interactions

- Other antihypertensives (increased hypotensive effect)

- Simvastatin – increased risk of myopathy therefore dose of statin should be reduced

- Antiepileptics (reduced efficacy of dihydropyridines)

- Digoxin (increased plasma digoxin concentration)

- Theophylline (increased plasma theophylline concentration)

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects

Efficacy: Reduction in blood pressure

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**Diltiazem**

**Drug Class:** Rate-limiting calcium channel blocker

**Other commonly used drugs in this class:** Verapamil

**Mode of Action**

![Diagram showing the mode of action of Diltiazem]

**Target:** L-type calcium channels - Diltiazem and Verapamil favour the hyperpolarised Ca\(^{2+}\) channels more commonly found in cardiac muscle cells

**Action:** Antagonist

**Effect:** Inhibit influx of calcium ions into cardiomyocytes through L-type calcium channels

**Overall effect:** Negative inotropic effect – decreases cardiac contractility

**Clinical indications:**

- Prophylaxis and treatment of angina
- Supraventricular arrhythmias
- Hypertension

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Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Diltiazem: 60mg three times daily, increase if necessary to 360mg daily

Verapamil: 40-120mg tid for supraventricular arrhythmias; 80-100mg for angina; 240-480mg daily for hypertension

Adverse effects

Common:

- Asthenia; AV block; bradycardia; constipation, (particularly in elderly patients)
- Dizziness; headache; hot flushes; hypotension; malaise; oedema (notably of ankles); palpitation; sino-atrial block

Important:

- Sino-atrial and AV block with diltiazem, particularly in those taking digoxin and/or beta blockers

Contra-indications and cautions

- Caution in heart failure, first degree AV block and bradycardia (avoid if severe)
- Avoid in second or third degree AV block, SA block, sick sinus syndrome, Wolff-Parkinson-White syndrome, hypotension and cardiogenic shock

Interactions

- Antihypertensives (increased hypotensive effect)
- Beta blockers (asystole, severe hypotension, heart failure)
- Anti-arrhythmics (increased risk of bradycardia, AV block and myocardial depression)

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects

Efficacy: Depends on indication e.g. reduced frequency of angina attacks, restoration to sinus rhythm

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Nicorandil

**Drug Class:** Potassium channel activator

**Mode of Action**

**Target:** ATP-sensitive K+ channels on the smooth muscle cell membrane

**Action:** Activator/Agonist

**Effect: Nicorandil has a dual mode of action**

**Potassium channel activator:** Opens ATP-dependent potassium channels, causing K+ to leave the cell. This results in hyperpolarisation of the cell membrane, closure of voltage-gated Ca2+ channels and a reduction in intracellular calcium.

**Nitrate like effect:** Stimulates guanylate cyclase enzymes to increase production of the second messenger cyclic GMP (cGMP). This inhibits the entry of calcium ions into the cell leading to reduced intracellular calcium levels.

**Overall effect:** The potassium channel activator effects of nicorandil promote vascular smooth muscle relaxation and vasodilatation in the arterial system leading to reduced afterload. The nitrate effects lead to dilatation in the systemic venous system and a reduction in preload. Direct vasodilatory effects on the coronary arteries are also seen.

**Clinical indications:**

- Long term treatment of chronic stable angina pectoris in patients with at least one of the following risk factors: previous MI / previous CABG / confirmed coronary heart disease AND LVH, LVdysfunction, diabetes mellitus, hypertension or peripheral vascular disease.

**Prescribing and Safety**

**Usual dose:** Initially 10mg BD, usual dose 10-20mg BD

**Adverse effects**

**Common:**

- Cutaneous vasodilation with flushing; dizziness; headache (especially on initiation, usually transitory); increase in heart rate (at high doses); nausea; rectal bleeding; vomiting; weakness
Important:

- Nicorandil can cause serious skin, mucosal, and eye ulceration; including gastrointestinal ulcers, which may progress to perforation, haemorrhage, fistula or abscess. Stop treatment if ulceration occurs and consider an alternative.

Contra-indications and cautions

- Caution in hypovolaemia and acute MI
- Avoid in hypotension, cardiogenic shock and left ventricular failure

Interactions

- Sildenafil, tadalafil, vardenafil (significantly increased hypotensive effect)

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects (usually minor)

Efficacy: Reduction in frequency of angina attacks

Patient communication

Patients should be warned not to drive or operate machinery while taking this medication until it is established that their performance is not affected.
**Enoxaparin**

**Drug Class:** Low molecular weight heparins (LMWH)

**Other commonly used drugs in this class:** Dalteparin, Tinzaparin

**Mode of Action**

**Target:** Antithrombin III (a serine protease inhibitor)

**Action:** Activate/stimulate

**Effect:** Inhibit factor Xa in the common pathway of the clotting cascade

**Overall effect:** Factor Xa is needed to convert prothrombin to thrombin, therefore LMWHs inhibit coagulation

**Clinical indications:**

- Prophylaxis of venous thromboembolism (VTE)
- Treatment of VTE before adequate oral anticoagulation (with warfarin) is established
- Treatment of acute MI and unstable coronary artery disease, PE, DVT.

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**Prescribing and Safety**

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
LMWHs are given by subcutaneous injection.

- Prophylaxis of DVT in surgical patients – 20mg 2 hours before surgery then 20mg every 24 hours (40mg if high risk e.g. orthopaedic surgery)
- Prophylaxis of DVT in medical patients – 40mg once daily
- Treatment of DVT/PE – 1.5mg/kg once daily
- Treatment of acute MI – initial dose 30mg, then 1mg/kg every 12 hours for up to 8 days

**Adverse effects - Important:**

- Haemorrhage If haemorrhage occurs it is usually sufficient to withdraw unfractionated or low molecular weight heparin, but if rapid reversal of the effects of the heparin is required, protamine sulfate is a specific antidote (but only partially reverses the effects of low molecular weight heparins).
- Heparin-induced thrombocytopenia (HIT) Clinically important heparin-induced thrombocytopenia is immune-mediated and does not usually develop until after 5–10 days; it can be complicated by thrombosis. Signs of heparin-induced thrombocytopenia include a 30% reduction of platelet count, thrombosis, or skin allergy. If heparin-induced thrombocytopenia is strongly suspected or confirmed, the heparin should be stopped and an alternative anticoagulant, such as danaparoid, should be given.
- Hyperkalaemia

**Contra-indications and cautions**

- Caution in the elderly, renal impairment, hepatic impairment (avoid if severe) and those with low body weight
- Avoid in haemophilia and other haemorrhagic disorders, thrombocytopenia, recent cerebral haemorrhage, severe hypertension, peptic ulcer disease, acute bacterial endocarditis, following major trauma and in patients with known hypersensitivity to heparins
- Discontinue if patient develops HIT

**Interactions**

- NSAIDs (increased risk of haemorrhage)
- ACE inhibitors, ARBs (increased risk of hyperkalaemia)
- Antiplatelet agents (increased risk of haemorrhage)

**Therapeutic drug monitoring**

**Safety:** Platelet counts should be checked via FBC at the start of treatment and regular monitoring may be needed if treatment >4 days, serum potassium should be measured at baseline and monitored regularly throughout treatment in those at increased risk of hyperkalaemia.

Patients at high risk of bleeding e.g. those with renal impairment may require additional monitoring of antifactor Xa activity.

Advise the patient to avoid OTC NSAIDS
Warfarin

**Drug Class:** Coumarin; Vitamin K antagonist

**Other commonly used drugs in this class:** None

**Mode of Action**

**Target:** Vitamin K epoxide reductase

**Action:** Competitive inhibitor

**Effect:** Prevents post-translational gamma-carboxylation clotting factors II, VII, IX and X

**Overall effect:** Depletion of active clotting factors II, VII, IX and X; this produces a potent anticoagulant effect

NB. The onset of warfarin's anticoagulant effect is delayed for several days until already formed active clotting factors have been degraded

**Clinical indications:**

- Prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation
- Prophylaxis after insertion of prosthetic heart valve
- Prophylaxis and treatment of venous thrombosis and pulmonary embolism
- Transient ischaemic attack (TIA)
Prescribing and Safety

Usual dose:

- Loading dose 5-10mg
- Daily maintenance dose 3-9mg at the same time each day
- Dose depends on patient’s prothrombin time (INR), wide interindividual variation in dose

Adverse effects

Common:

- Haemorrhage and bruising

Important:

- Skin necrosis, hypersensitivity, liver dysfunction, jaundice, pyrexia

Contra-indications and cautions

- Caution in patients who have undergone recent surgery, those taking other drugs which increase the risk of bleeding and those with renal impairment (avoid if severe)
- Avoid in pregnancy, peptic ulcer disease, severe hypertension and those with hepatic impairment (especially if prothrombin time already prolonged)

Therapeutic drug monitoring

Safety: All patients on warfarin must have their International Normalised ratio (INR) checked regularly (this is ratio of the patient’s prothrombin time:reference standard blood prothrombin time). At the beginning of treatment this should be done every day or on alternate days then at progressively longer intervals of up to 12 weeks when a steady INR is achieved

Efficacy: INR

Patient communication

- Do not take any OTC medications (especially ASPIRIN) without checking with pharmacist as could interact with warfarin
- Inform anyone who wants to start you on a new medication that you are already taking warfarin

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
- For women of childbearing age – you must use reliable contraception while on warfarin as it is damaging in pregnancy

- Avoid drinking cranberry juice and major changes to diet including changes in the level of consumption of leafy green vegetables while on warfarin

- Avoid excessive alcohol consumption whilst on warfarin – do not need to avoid completely but drink in moderation and avoid 'binges'

- You will need to attend the doctor for a regular blood test to check the INR (this allows your doctor to determine the correct and safe dose for you) – this will be done daily or on alternate days in the early days of treatment, then at longer intervals of up to 12 weeks depending on your response

- Take warfarin at the same time every day

**Additional comments**

As the onset of the anticoagulant effect of Warfarin is delayed by several days, patients should be given a LMWH to cover them during this period.

**Interactions:**

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<th>Reduced anticoagulant effect</th>
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<td>Anti-arrhythmics – amiodarone, propafenone</td>
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<td>Antibacterials – chloramphenicol, ciprofloxacin, co-trimoxazole, erythromycin, metronidazole, ofloxacin and sulphonamides. Experience from anticoagulant clinics suggests that any broad-spectrum antibiotic, especially ampicillin, can increase the INR.</td>
<td>Vitamin K – high intake of vitamin K can counteract warfarin activity</td>
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**Rivaroxaban**

**Drug Class:** Factor Xa inhibitors

**Other commonly used drugs in this class:** Apixaban, Edoxaban

**Mode of Action**

**Target:** Factor Xa

**Action:** Competitive inhibition

**Effect:** Inhibits activated factor Xa, which is required for the conversion of prothrombin to thrombin in the common pathway of the coagulation cascade

**Overall effect:** Lack of thrombin prevents conversion of fibrinogen to fibrin and therefore inhibits thrombus formation

NB. Another recently introduced oral anticoagulant is Dabigatran, a direct thrombin (factor II) inhibitor. This drug is a competitive inhibitor of thrombin and therefore prevents conversion of fibrinogen to fibrin, inhibiting thrombus formation.

**Clinical indications:**

Prophylaxis of venous thromboembolism (VTE) following hip/knee replacement surgery

Treatment of DVT & prophylaxis of recurrent DVT & PE
Prescribing and Safety

Rivaroxaban – 10mg once daily for 2 weeks after knee replacement (5 weeks after hip replacement)
Dabigatran – 220mg once daily for 9 days after knee replacement (27-34 days after hip replacement)
Reduce dose in renal impairment

Adverse effects:

Common:
- Haemorrhage (no reversal agent licensed at present)
- Abdominal pain; constipation; diarrhoea; dizziness; dyspepsia; headache; hypotension; nausea; pain in extremities; pruritus; rash; renal impairment; vomiting

Important:
- Hepatobiliary disorders (dabigatran)

Contra-indications and cautions
- Caution in the elderly, patients weighing <50kg, active or recent GI ulceration and those with bleeding disorders
- Avoid in active bleeding and in severe renal or hepatic impairment, pregnancy and breast-feeding.
- Discontinue if severe bleeding occurs

Interactions
- NSAIDs (increased risk of bleeding)
- Amiodarone (increased plasma dabigatran concentration – reduce dose of dabigatran)
- Verapamil (increased plasma dabigatran concentration – reduce dose of dabigatran)
- Triazole antifungals (avoid combination with rivaroxaban)

Therapeutic drug monitoring
Safety: Monitor for signs of bleeding or anaemia, routine coagulation profile monitoring NOT recommended, monitoring of renal function in those with renal impairment may be necessary

Efficacy: Prevention of DVT/PE

Additional information:

These novel anticoagulants have a much broader therapeutic index than the traditionally-used oral anticoagulant warfarin – this allows for fixed drug dosing without the need for coagulation monitoring. However, at present no specific antidotes to these drugs exist.

Tablets should be taken with food.

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Aspirin

**Drug Class:** Antiplatelet agents

**Mode of Action**

**Target:** Cyclooxygenase enzymes

**Action:** Irreversible inhibitor

**Effect:** Impairs synthesis of thromboxane A$_2$ and prostacyclin within platelets

**Overall effect:** Reduced platelet aggregation

**Clinical indications:**

**Primary prevention of cardiovascular disease with aspirin:**

- Is no longer recommended

**Secondary prevention of cardiovascular disease following:**

- MI/acute coronary syndrome/angina pectoris
- Stroke
Prescribing and Safety

75mg once daily

Adverse effects:

Important:
- GI irritation, ulceration and bleeding
- Bronchospasm

Contra-indications and cautions
- Caution in asthma, uncontrolled hypertension and previous peptic ulceration
- Avoid in active peptic ulceration, haemophilia and other bleeding disorders and those with known hypersensitivity to aspirin or other NSAIDs

Interactions

Increased bleeding risk with: NSAIDs, Anticoagulants, SSRIs

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects

Patient communication:

Advise patients that aspirin tablets should be taken whole without chewing. Also explain that patients should not take indigestion remedies at the same time of day as this medication. It should be taken with or after food to minimise risk of GI irritation.

Advise patients that aspirin must not be given to children under the 12 due to the risk of Reye’s syndrome.

Additional information:

If the patient requires aspirin but is at high risk of GI bleeding, a PPI can be co-prescribed to reduce this risk.

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**Clopidogrel**

**Drug Class:** ADP receptor pathway inhibitors (antiplatelets)

**Mode of Action**

**Target:** ADP Receptor  
**Action:** Irreversible Inhibitor  
**Effect:** Inhibits binding of adenosine diphosphate (ADP) to its platelet receptor  
**Overall effect:** Inhibits platelet aggregation

**Clinical indications:**
- Secondary prevention of atherothrombotic events e.g. following MI or ischaemic stroke or peripheral arterial disease  
- With aspirin in acute coronary syndrome and for 1 year following procedures to the coronary arteries
Prescribing and Safety

Secondary prevention following MI/stroke: 75mg once daily
Acute coronary syndrome: Loading dose – 300-600mg
     Maintenance dose – 75mg daily

Adverse effects:
Common:
• GI disturbance (dyspepsia, abdominal pain, diarrhoea); bleeding disorders (including GI and intracranial)

Important:
• Gastric and duodenal ulcers

Contra-indications and cautions
• Caution in hepatic and renal impairment (avoid if severe) and those at increased risk of bleeding e.g. due to trauma, surgery, uncontrolled hypertension or with other medications which increase bleeding risk
• Avoid in pregnancy
• Avoid in active bleeding
• Discontinue clopidogrel 7 days before elective surgery

Interactions
• Other antiplatelet drugs (increased risk of bleeding)
• Anticoagulants (increased risk of bleeding) – especially warfarin
• Fibrinolytics (increased risk of bleeding)
• Ulcer healing drugs (reduced antiplatelet effect)
• NSAIDs: Increased risk of bleeding

Therapeutic drug monitoring
Safety: Monitor patients for side effects

Patient communication: Inform pharmacist if purchasing over-the-counter treatment that he/she is taking clopidogrel.

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Dipyridamole

Drug Class: Anti-platelet

Mode of Action: Unclear, likely involves a number of anti-platelet actions

Effects:

1. Reversible Inhibitor of platelet phosphodiesterase, and consequently cyclic AMP concentration is increased and platelet activity reduced.
2. Blocks adenosine uptake into RBCs, thus increasing plasma adenosine levels which has a vasodilatory and anti-platelet effect
3. Potentiation of PGI2 anti-aggregatory activity and enhancement of PGI2 biosynthesis

Overall effect: Reduced platelet activation and aggregation

Clinical indications:

- With warfarin in thromboembolic prophylaxis in patients with prosthetic heart valves
- With aspirin in secondary prevention of ischaemia stroke and TIA

Prescribing and Safety

300-600mg daily in 3-4 divided doses (less for modified release)

Adverse effects:

Common: GI disturbance

Important:

- Haemorrhage; Hypotension; Worsening symptoms of coronary artery disease

Contra-indications and cautions

- Caution in rapidly worsening angina, aortic stenosis, recent MI, LV outflow obstruction, heart failure, hypotension, patients with coagulation disorders and those taking other drugs which increase risk of bleeding

Interactions

- Adenosine (enhances and extends cardiovascular effects - important risk of toxicity)
- Other antiplatelets (increased risk of bleeding)
- Anticoagulants (increased risk of bleeding)
- Fibrinolytics (increased risk of bleeding)

Therapeutic drug monitoring

Safety: Monitor for side effects

Patient communication:

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Patients should be advised to take this medication 30 minutes to an hour before food OR for modified release preparations – take with or after food and swallow whole without chewing.

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**Simvastatin**

**Drug Class:** HMG Co-enzyme A reductase inhibitors (lay terminology abbreviation: statins)

**Other commonly used drugs in this class:** Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin

**Mode of Action**

**Target:** HMG Co-enzyme A reductase (rate-limiting enzyme in cholesterol biosynthesis)

**Action:** Competitive inhibitor

**Effect:** Inhibition of HMG Co-enzyme A reductase reduces hepatic cholesterol synthesis through the mevalonate pathway. This in turn leads to upregulation of the LDL-receptors and increased hepatic removal of LDL from the circulation.

**Overall effect:** Reduce LDL cholesterol, reduce triglycerides, increase HDL cholesterol

**Clinical indications:**

- Treatment of primary hypercholesterolaemia
- Treatment of homozygous familial hypercholesterolaemia
- Prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or diabetes mellitus
Prescribing and Safety

20-40mg nocte (up to 80mg in primary hypercholesterolaemia and homozygous familial hypercholesterolaemia)

Adverse effects

Common:
- Abnormal LFTs (elevated transaminases); GI disturbance e.g. constipation, flatulence, myalgia

Important:
- Myositis, rhabdomyolysis – factors which increase risk include high dose, low body mass, hypothyroidism, alcohol and combination with a fibrate (esp. Gemfibrozil)

Contra-indications and cautions

- Caution in patients with risk factors for myositis/rhabdomyolysis (see above) and those with history of liver disease
- Avoid in active liver disease and pregnancy
- Discontinue if serum transaminases become elevated >3x ULN or patient develops severe muscular symptoms +/- creatine kinase elevated>5x ULN

Interactions

Increased risk of myopathy when statins given alongside:

Amiodarone; calcium channel blockers; fibrates, particularly gemfibrozil; antibiotics; antifungals; antivirals; colchicine.

Statins, particularly simvastatin, may increase the anticoagulant effect of warfarin.

Therapeutic drug monitoring

Safety: LFTs should be checked at baseline and every 3 months during treatment. If rhabdomyolysis is suspected check creatine kinase (CK) level. TFTs, CK, HbA1c and U&E should also be assessed at baseline.

Efficacy: Improvement in lipid profile (reduced non-HDL and LDL cholesterol)

Patient communication

Advise patients to promptly report any unexplained muscle pain, tenderness or weakness; likewise for shortness of breath, cough and weight loss.

Female patients should be advised to use reliable contraception for the duration of treatment and for one month after stopping a statin.
Respiratory system

Salbutamol

**Drug Class:** Short acting beta 2 agonist

**Other commonly used drugs in this class:** Terbutaline

**Mode of Action**

![Diagram showing mode of action](image)

**Target:** β₂ adrenoceptors in bronchial smooth muscle

**Action:** Agonist

**Effect:** Activation of β₂ adrenoceptors stimulates adenylate cyclase enzymes to increase production of cyclic AMP (cAMP).

**Overall effect:** Bronchial smooth muscle relaxation and bronchodilatation

**Clinical indications:**

Asthma and other conditions associated with reversible airways obstruction e.g. COPD.
Prescribing and Safety

- By aerosol inhalation (inhaler) – 100-200micrograms (1-2 puffs) up to 4 times daily as required to control symptoms
- By inhalation of nebulised solution – 2.5-5mg repeated up to 4 times daily
- By inhalation of powder – 200-400micrograms up to 4 times daily
- By mouth – 2-4mg 3-4 times daily, maximum single daily dose 8mg

Adverse effects

Common:
- Fine tremor; Headache; Muscle cramps; Palpitations

Important:
- Arrhythmias; Myocardial ischaemia; Hypokalaemia (high doses); Lactic acidosis (high doses)

Contra-indications and cautions

- Caution in diabetes mellitus, hyperthyroidism and cardiovascular disease including arrhythmias and hypertension

Therapeutic drug monitoring

Safety: Monitor serum potassium if giving a high dose, particularly those also taking drugs such as theophylline, corticosteroids and diuretics

Efficacy: Resolution of symptoms/acute attack. If β₂ agonist is required more than twice a week or if symptoms disturb sleep more than once a week or if patient has suffered an exacerbation, then prophylactic treatment should be considered using a stepped approach.

Patient communication

Explain to patients that salbutamol is the ‘reliever inhaler/medication’ and should be used when they experience their asthma symptoms - it will not prevent attacks.

Explain to patients taking salbutamol by aerosol inhalation (most common route) that it is important to have good inhaler technique in order to get maximum benefit from the medication – patients should ideally be shown how to use the inhaler and then observed to ensure their technique is correct.

Patients should take immediately before exercises to reduce exercise induced asthma

Additional comments

Patients who are having difficulty with their inhaler technique may benefit from the use of a spacer device, dry powder inhaler or breath activated inhaler.
**Tiotropium bromide**

**Drug Class:** Inhaled antimuscarinics/ anticholinergic (long acting muscarinic antagonist LAMA)

**Other commonly used drugs in this class:** Ipratropium bromide (short acting muscarinic antagonist SAMA); other LAMA: aclidinium bromide, umeclidinium bromide

**Mode of Action**

**Target:** Muscarinic (M₃) receptors

**Action:** Competitive antagonist

**Effect:** Compete with endogenous ligand acetylcholine (ACh) for binding sites on muscarinic receptors in bronchial smooth muscle. This prevents ACh-mediated constriction of the bronchi.

**Overall effect:** Bronchial smooth muscle relaxation and bronchodilatation

**Clinical indications:**

- Reversible airways obstruction, particularly in COPD

**NB.** Tiotropium, aclidinium and umeclidinium are long acting LAMA agent therefore are **NOT APPROPRIATE IN ACUTE BRONCHOSPASM.**
Prescribing and Safety

Ipratropium: 20-40 micrograms 3-4 times daily (250-500 micrograms if inhaling nebulised solution)

Tiotropium: 5 micrograms once daily (Respimat®) (18 micrograms once daily if given by powder inhalation (Spiriva®)

Adverse effects

Common:
- Dry mouth; Nausea; Headache; constipation; cough; diarrhoea; sinusitis; epistaxis; oral candidiasis; taste disturbance

Important:
- Atrial fibrillation; Acute angle closure glaucoma; Urinary retention; paradoxical bronchospasm, blurred vision, GORD, dental caries

Contra-indications and cautions

- Caution in prostatic hyperplasia, bladder outflow obstruction and those at risk of angle-closure glaucoma

Interactions

- Interactions do not generally apply to antimuscarinics used by inhalation. Concomitant use of 2 or more drugs with anti-muscarinic properties increases risk of adverse drug effects.

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects

Efficacy: Improvement in symptoms

Patient communication

Advise patients that they should not exceed the prescribed daily dose.

Explain to patients taking these drugs by inhaler that it is important to have good inhaler technique in order to get the most from this medication – patients should ideally be shown how to use the inhaler and then observed to ensure their technique is correct. Reminded that powder inhalation capsules are not for oral administration.

Additional comments

Patients who are having difficulty with their inhaler technique may benefit from the use of a spacer device, dry powder inhaler or breath activated inhaler.
**Montelukast**

**Drug Class:** Leukotriene receptor antagonists (LTRA)

**Other commonly used drugs in this class:** Zafirlukast

**Mode of Action**

**Target:** Cysteinyl leukotriene receptor CysLT1

**Action:** Antagonist

**Effect:** Block the action of cysteiny1 leukotrienes (pro-inflammatory eicosanoids released from mast cells and eosinophils) in airway smooth muscle

**Overall effect:** Reduce the airway inflammation seen in asthma and rhinitis

**Clinical indications:**

- Management of persistent poorly controlled asthma (step 4 in the BTS guidelines)
- Symptomatic relief of seasonal allergic rhinitis in asthma patients
- May be of particular benefit in exercise-induced or aspirin-induced asthma

**Prescribing and Safety**

Montelukast: 10mg once daily in the evening

Zafirlukast: 20mg twice daily

**Adverse effects**

**Common:**

- Abdominal pain; headache; hyperkinesia (in young children); thirst
Important:

- Churg-Strauss syndrome (very rare but watch out for eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy)
- Hypersensitivity (including anaphylaxis and angioedema)
- Depression, suicidal thoughts and behaviour
- Seizures
- Agranulocytosis / hepatotoxicity with zafirlukast

Contra-indications and cautions

- Caution in the elderly and those with renal impairment
- Avoid in hepatic impairment

Interactions

- Warfarin (increased anticoagulant effect)

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects

Efficacy: Reduction in frequency of asthma attacks, improvement in peak expiratory flow rates (PEFR)

Patient communication

Ensure patient is aware that these are for long term prophylaxis NOT FOR ACUTE EXACERBATIONS

Patients and prescribers should be aware of the signs of Churg-Strauss syndrome including development of vasculitic rash, worsening pulmonary symptoms, cardiac complications and peripheral neuropathy.

Patients taking zafirlukast should be advised to seek medical advice if they notice any symptoms/signs of infection, especially sore throat, due to the risk of agranulocytosis.

If taking Singular (Montelukast) granules, these should be swallowed or mixed with cold food (not fluid) and taken immediately.

If taking zafirlukast, patients or their carers should be told how to recognise development of liver disorder and advised to seek medical attention if symptoms or signs such as persistent nausea, vomiting, malaise or jaundice develop.
Chlorphenamine

Drug Class: Antihistamines

Other commonly used drugs in this class: Cetirizine, Fexofenadine, Loratadine, Promethazine

Mode of Action

Target: Histamine H<sub>1</sub> receptor

Action: Competitive antagonist

Effect: Competes with histamine for binding sites on the H<sub>1</sub> receptor

Overall effect: Blocks the acute inflammatory effects of histamine e.g. vasodilatation, increased vascular permeability (see diagram for more details)

Clinical indications:

- Symptomatic relief in seasonal allergic rhinitis
- Urticaria
- Pruritus
- Emergency treatment of anaphylactic reactions (chlorphenamine)
Prescribing and Safety

Chlorphenamine – 4mg every 4-6 hours, maximum 24mg daily

Cetirizine, Loratadine – 10mg once daily

Promethazine – 10-20mg 2-3 times daily

Adverse effects

Common:
- Drowsiness, particularly with chlorphenamine and promethazine (sedating antihistamines)
- Blurred vision; dry mouth; GI disturbance; headache; pscyhomotor impairment and urinary retention

Important:
- Extrapyramidal effects
- Hypersensitivity reactions including bronchospasm, angioedema, anaphylaxis and rashes

Contra-indications and cautions

- Sedating antihistamines have significant antimuscarinic activity – use with caution in prostatic hyperplasia, urinary retention, pyloroduodenal obstruction and those at risk of angle-closure glaucoma; also caution in epilepsy
- Avoid in severe liver disease, pregnancy and breastfeeding

Interactions

- Antidepressants e.g. MAOIs, tricyclics (increased sedative and antimuscarinic effects)

Therapeutic drug monitoring

Safety: None

Efficacy: Improvement/resolution of allergic symptoms, itch, etc.

Patient communication

Advise patients that this medication can cause drowsiness which may impair their ability to drive and operate machinery. If this happens they should avoid these activities until the effects have worn off.
**Pseudoephedrine**

**Drug Class:** Systemic nasal decongestants

**Other commonly used drugs in this class:** None

**Mode of Action**

**Target:** Alpha and beta adrenoceptors

**Action:** Agonist

**Effect:** Alpha adrenoceptors – pseudoephedrine binds to $\alpha$ receptors in the respiratory mucosa causing vascular smooth muscle contraction and vasoconstriction

Beta adrenoceptors – pseudoephedrine binds to $\beta_2$ receptors in bronchial smooth muscle leading to bronchodilatation

**Overall effect:** Relief of nasal and sinus congestion

**Clinical indications:**

- Nasal congestion
- Sinus congestion

**Prescribing and Safety**

60mg 3-4 times daily

**Adverse effects**

**Common:**

- Anxiety; headache; hypertension; insomnia; nausea; restlessness; tachycardia; vomiting

**Important:**

- Hallucinations; angle-closure glaucoma and urinary retention
Contra-indications and cautions

- Caution in diabetes, hypertension, hyperthyroidism, IHD, prostatic hypertrophy and those at risk of angle-closure glaucoma

Interactions

- Alpha blockers (reduced hypotensive effect)
- **MAOIs (risk of hypertensive crisis – do not co-preserve)**

Therapeutic drug monitoring

Safety: None

Efficacy: Improvement/resolution of symptoms

NB: In some countries OTC access to pseudoephedrine has been stopped due to the potential for its misuse in the synthesis of metamphetamine/crystal meths

Patient communication

Can cause insomnia, therefore do not take late at night

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Central nervous system

Diazepam

**Drug Class:** Benzodiazepines

**Other commonly used drugs in this class:** Lorazepam, Oxazepam, Temazepam

**Mode of Action**

**Target:** Benzodiazepine (BDZ) receptor on GABA-BDZ receptor complex

**Action:** Agonist

**Effect:** Increase affinity of the inhibitory neurotransmitter GABA for the GABA<sub>A</sub> receptor – this causes post-synaptic chloride ion channels to open

**Overall effect:** Increased flow of negative chloride ions into the neurone leading to hyperpolarisation of the membrane – this prevents further excitation

**Clinical indications:**

- Short term treatment of severe anxiety
- Short term treatment of insomnia
- Muscle spasm/spasticity
- Status epilepticus
**NB.** Non-benzodiazepine hypnotics e.g. zolpidem, zopiclone — these drugs bind with high selectivity to the α1 subunit of the GABA<sub>A</sub> receptor/chloride ion channel complex. As such they have strong hypnotic activity but negligible anxiolytic, myorelaxant and anticonvulsant properties. They are for short term use only (up to 4 weeks).

Benzodiazepines are classified into short acting and long acting, based on their half-lives. Short acting benzodiazepines are typically used as anxiolytics e.g. alprazolam, longer acting benzodiazepines as hypnotics e.g. diazepam.

**Prescribing and Safety**

Diazepam – 2mg tid increased if necessary to 15-30mg daily in divided doses (half dose in elderly)

**Adverse effects:**

**Common:**
- Amnesia, ataxia (especially elderly); confusion; dependence, drowsiness and dizziness the next day (hang-over effect)
- Psychomotor impairment

**Important:**
- Ataxia leading to increased risk of falls in the elderly
- Physical and psychological dependence
- Respiratory depression
- Tolerance

**Contra-indications and cautions**
- Caution in the elderly, patients with respiratory disease, muscle weakness, myasthenia gravis (avoid if unstable) and those with a history of drug or alcohol abuse
- Avoid in patients with respiratory depression, marked neuromuscular weakness, acute pulmonary insufficiency, sleep apnoea syndrome, pregnancy and breastfeeding
- Should not be used for greater than 4 weeks

**Interactions**
- Antihypertensives (enhanced hypotensive effect)
- Clozapine (serious adverse effects reported with lorazepam)

**Therapeutic drug monitoring**

**Safety:** Monitor clinically for adverse effects — in hospitalised patients respiratory rate and oxygen saturations should be monitored

**Efficacy:** Depends on clinical indication e.g. improvement/resolution of symptoms of anxiety
Patient communication:
Explain to patients that this medication may impair their ability to perform skilled tasks such as driving and may cause drowsiness.

Advise patients that their medication enhances the effects of alcohol.

Additional information
The effects of benzodiazepine overdose can be reversed by giving intravenous flumazenil, however the danger from inducing status epilepticus and death when using flumazenil as an antidote/reversal agent in the overdose situation prevents its use in this area. Withdrawal of long term benzodiazepine use is challenging and requires a supportive environment with gradual reduction of benzodiazepine dose over a protracted period of time.
Antipsychotics

Mode of Action

**Typical antipsychotics e.g. haloperidol, chlorpromazine, Prochlorperazine** work as follows:

**Target:** Muscarinic, histamine, dopamine, serotonin and adrenergic receptors

**Action:** Mixed antagonists – main action is through antagonism of dopamine D₂ receptors

**Effect:** Reduced release of dopamine from dopaminergic nerve terminals, reduced electrical activity in dopaminergic neuronal pathways – action on mesolimbic/mesocortical pathways is responsible for the antipsychotic activity of these drugs, while action on the nigrostriatal pathways produces the unwanted side effects

**Atypical antipsychotics e.g. risperidone, quetiapine, clozapine** are also antagonists at dopamine D₂ receptors. However, they may also block serotonin 5-HT₂ receptors and/or α-adrenoceptors. They are licensed for use in newly diagnosed schizophrenia, management of an acute schizophrenic episode and as an alternative in patients who cannot tolerate a conventional antipsychotic. They are more useful in treating the negative symptoms of schizophrenia.

**Clinical indications:**

- Schizophrenia and other psychoses; Mania

**Prescribing and Safety**

Haloperidol – starting dose 0.5-3mg 2-3 times daily; maintenance dose 5-30mg daily

Chlorpromazine – 10-25mg every 4-6 hours (reduce in severe renal impairment due to increased cerebral sensitivity)

Risperidone – 1-6mg daily in divided doses

Clozapine – 200-450mg daily in divided doses

**Adverse effects**

**Common:**

- Drowsiness, sedation; Agitation

**Important:**

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
- Extrapyramidal symptoms; Postural hypotension – risk of falls in the elderly; Tardive dyskinesia (may be irreversible); Neuroleptic malignant syndrome; Agranulocytosis (clozapine only)

**Contra-indications and cautions**

- Caution in cardiovascular disease, diabetes, Parkinson’s disease and hepatic impairment
- Avoid in CNS depression and coma

**Interactions**

- Antihypertensive agents (increased hypotensive effect)
- Drugs that prolong QT interval (increased risk of arrhythmias including torsades de pointes)
- Antiepileptics (lower the seizure threshold)
- Opioids (increased CNS depression/sedation)
- Alcohol (increased CNS depression)

**Therapeutic drug monitoring**

**Safety:** Monitor patient clinically for adverse effects. With clozapine an FBC should be performed at baseline and re-checked every week for the first 18 weeks then every 2 weeks thereafter.

**Efficacy:** Improvement in symptoms

**Patient communication**

Explain to patients that this medication may cause drowsiness and could impair their ability to perform skilled tasks such as driving. It also enhances the effects of alcohol and care should be taken in this regard.

**Additional comments**

Prescribing more than one antipsychotic drug at any one time is not recommended.

There is a high risk of relapse if these drugs are stopped after 1-2 years of therapy. Antipsychotics should be withdrawn gradually to avoid acute withdrawal syndromes and/or relapse and patients should be closely monitored during this period and for 2 years afterwards.

If these drugs are effective but patient compliance is poor, consider using depot preparations. Antipsychotics should not be used as hypnotics.
**Lithium**

**Drug Class:** Mood stabilisers

**Mode of Action**

Unclear & complex, involves:

- Reduced activity of sodium dependent intracellular second messenger systems
- Modulation of dopamine and serotonin pathways
- Reduced activity protein kinase C
- Reduced arachidonic acid turnover
- ?Neuroprotective effects?

**Clinical indications:**

- Mania; Bipolar disorder

**Prescribing and Safety**

**Adverse effects:**

**Common:**
- GI upset; Fine tremor; Weight gain

**Important:**
- Hypothyroidism
- Hyperparathyroidism, hypercalcaemia
- **Lithium toxicity** – blurred vision, muscle weakness, drowsiness, coarse tremor, slurred speech, ataxia, confusion, convulsions, nausea, vomiting and ECG changes

**If toxicity is suspected:**
- Stop lithium immediately
- Check lithium levels, serum creatinine, U&E
- Refer to A&E if clinically necessary
- Seek advice from psychiatry for re-initiation of lithium

**Contra-indications and cautions**

- Caution in the elderly and those with psoriasis and myasthenia gravis
- Avoid in serious cardiac disease (heart failure, sick sinus syndrome), Addison’s disease, renal impairment (if possible), pregnancy and breastfeeding
- Reduce dose or discontinue lithium in diarrhoea, vomiting and intercurrent infection (especially if patient is sweating profusely)
• Discontinue lithium 24 hours before surgery and restart as soon as renal function and fluid balance are back to normal

**Interactions**
• The following drugs increase lithium levels: antibiotics metronidazole, tetracyclines and co-trimoxazole; NSAIDs, ACE inhibitors, ARBs and diuretics
• The following drugs decrease lithium levels: xanthines theophyllines, aminophylline and caffeine; sodium salts and acetazolamide
• Amiodarone (increased risk of ventricular arrhythmias)

**Therapeutic drug monitoring**

**Safety:** Baseline measurements should include U&E, eGFR, free T4, TSH, weight and height (plus FBC and ECG if indicated). Then:

• Every 3 months – serum lithium level (normal therapeutic range 0.4-1.0mmol/l, set target for each patient)
• Every 6 months – fT4, TSH, U&E and eGFR
• Every 12 months – check height and weight (BMI)

Monitor more frequently in elderly patients and after dose changes. Also assess for side effects, altered risk factors and signs of lithium toxicity at every consultation and refer to renal or endocrinology services if needed.

**Efficacy:** Improvement in symptoms/mental state

**Patient communication:**
Patients should be given a lithium treatment pack on initiating therapy, consisting of a patient information leaflet, lithium alert card and monitoring record book which they should bring to each appointment.
Explain to patients the importance of maintaining adequate fluid intake and avoiding dietary changes which increase or decrease sodium intake. This medication should be swallowed whole without chewing.
Advise patients that they must not stop taking their medication suddenly as there is a strong chance of manic relapse. If withdrawing lithium, doctors should do this gradually and monitor patient for signs of relapse.

**Additional information:**
Lithium must be prescribed by brand, NOT generically as preparations vary widely in bioavailability. Once stabilised, patients should be maintained on the same brand.
When checking serum lithium levels, blood samples must be taken 12 hours after the latest dose.

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**Amitriptyline**

**Drug Class:** Tricyclic antidepressants (TCAs)

**Other commonly used drugs in this class:** Dosulepin, Imipramine, Nortriptyline

**Mode of Action**

**Target:** Noradrenaline and serotonin reuptake transporters on the pre-synaptic neuronal membrane

**Action:** Inhibitor

**Effect:** Prevent re-uptake and subsequent degradation of the monoamine neurotransmitters serotonin and noradrenaline from the synaptic cleft

**Overall effect:** Prolonged presence of serotonin and noradrenaline in the synaptic cleft leads to prolonged neuronal activity – in mood disorders such as depression there are low levels of these neurotransmitters in the brain. TCAs therefore restore the concentration to normal levels.

**Clinical indications:**

- Depressive illness (not recommended as first line therapy); Neuralgia; Nocturnal enuresis in children; Migrane prophylaxis (unlicensed)

**Prescribing and Safety**

Starting dose – 75mg daily (30-75mg if elderly) (lower doses for indications other than depression)in divided doses or as a single dose nocte

Maintenance dose – varies depending on drug; for amitriptyline 150-200mg

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Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Adverse effects:

Common:
- Abdominal pain; fatigue; hypertension; mydriasis; oedema; palpitation; restlessness; stomatitis
- Antimuscarinic effects – dry mouth, blurred vision, constipation, urinary retention
- CNS side effects (particularly in elderly) e.g. anxiety, dizziness, agitation, confusion
- Weight gain

Important:
- **Cardiotoxic in overdose – caution in patients at risk of suicide
- Neuroleptic malignant syndrome
- Hyponatraemia (particularly in elderly)

Contra-indications and cautions
- Caution in cardiovascular disease, hepatic impairment (avoid if severe), hyperthyroidism, epilepsy, diabetes, prostatic hypertrophy, chronic constipation, urinary retention, glaucoma, the elderly and those at high risk of falls and of suicide
- Avoid following MI, in heart block and in the manic phase of bipolar disorder
- Discontinue if patient enters a manic phase

Interactions
- **MAOIs (risk of hypertensive crisis and hyperthermia) – do not start a tricyclic until 2 weeks after stopping an MAOI and vice versa, do not co-prescribe
- Antiepileptics (seizure threshold lowered)
- Alcohol (increased sedative effect)
- Anti-arrhythmics (increased risk of ventricular arrhythmias)

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects

Efficacy: Improvement in mood, resolution of symptoms

Patient communication:
Explain to patients that this medication can cause drowsiness which may affect their ability to drive and operate machinery – if this happens they should avoid these activities until the effects wear off. Patients should also be advised to avoid, or at least minimise consumption of, alcohol as this medication enhances its effects.

Encourage patients to keep going with treatment in spite of side effects (within reason) as a degree of tolerance to these effects often develops.
**Additional information:**

Elderly patients are more prone to many of the TCA side effects – these patients should be monitored more closely, particularly for psychiatric and cardiac effects.

Doctors should prescribe only limited quantities of TCAs at any one time due to their cardiotoxicity and relatively high rate of fatality in overdose.

TCAs in overdose cause coma / convulsions and cardiac dysrhythmias, refer to toxbase for management which includes supportive care, cardiac monitoring, neurological observation, sodium bicarbonate as the pharmacological treatment of the overdose.

If TCAs need to be withdrawn this should be done slowly where possible due to the risk of withdrawal symptoms e.g. flu-like symptoms, insomnia, mania, cardiac arrhythmia.
Fluoxetine

**Drug Class:** Selective serotonin reuptake inhibitors (SSRIs)

**Other commonly used drugs in this class:** Citalopram, Escitalopram, Paroxetine, Sertraline

**Mode of Action**

**Target:** Serotonin re-uptake transporter on the pre-synaptic neuronal membrane

**Action:** Inhibitor

**Effect:** Prevents re-uptake and subsequent degradation of the monoamine neurotransmitter serotonin from the synaptic cleft

**Overall effect:** Prolonged presence of serotonin in the synaptic cleft leads to prolonged neuronal activity – in mood disorders such as depression there are low levels of this neurotransmitter in the brain. SSRIs therefore restore the concentration of serotonin to normal levels.

**Clinical indications:**

- Depressive illness
- Panic disorder
- Obsessive compulsive disorder

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Adverse effects:

Common:
- GI upset (dose related) – nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation
- Anorexia with weight loss
- Increased risk of bleeding

Important:
- Hypersensitivity reactions – rash, urticaria, angioedema, anaphylaxis
- Convulsions
- Neuroleptic malignant syndrome
- Risk of withdrawal effects so withdraw gradually

Contra-indications and cautions
- Caution in patients with epilepsy (discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle closure glaucoma, history of mania or bleeding disorders, hepatic or renal impairment, those taking other drugs which increase risk of bleeding and those received concomitant electroconvulsive therapy
- Avoid in pregnancy
- Discontinue SSRIs if the patient enters a manic phase

Interactions
- Alcohol (increased sedative effect)
- NSAIDs (increased risk of bleeding)
- Antiepileptics (SSRIs lower the seizure threshold)
- Theophylline (half theophylline dose or avoid where possible)
- MAOIs – SSRIs should not be started until 2 weeks of stopping an MAOI, MAOIs should not be started until 7-14 days after stopping an SSRI

Therapeutic drug monitoring

Safety: Monitor for side effects, if confusion or falls occur, check U+E for a serum sodium concentration (rule out hyponatraemia)

Efficacy: Depends on clinical indication e.g. improvement/resolution of symptoms of depression

Patient communication:
Explain to patients that this medication may impair their ability to perform skilled tasks such as driving and may cause drowsiness.
**Venlafaxine**

**Drug Class:** Serotonin/noradrenaline reuptake inhibitors

**Other commonly used drugs in this class:** Duloxetine

**Mode of Action**

![Mode of Action Diagram]

**Target:** Serotonin and noradrenaline re-uptake transporters on the pre-synaptic neuronal membrane

**Action:** Inhibitor

**Effect:** Prevents re-uptake and subsequent degradation of the monoamine neurotransmitters serotonin and noradrenaline from the synaptic cleft

**Overall effect:** Prolonged presence of serotonin and noradrenaline in the synaptic cleft leads to prolonged neuronal activity – in mood disorders such as depression there are low levels of these neurotransmitters in the brain. Serotonin/noradrenaline reuptake inhibitors therefore restore the concentration to normal levels.

**Clinical indications:**

- Major depressive disorder
- Generalised anxiety disorder
- Duloxetine is also used for stress incontinence
Prescribing and Safety

Venlafaxine:
Starting dose – 75mg daily in 2 divided doses
Maintenance dose – up to maximum 375mg daily (half dose in hepatic or renal impairment)

Duloxetine:
Starting dose – 30mg daily
Maintenance dose – usually 30-60mg daily, maximum 120mg daily

Adverse effects:
Common:
- Large number of central and peripheral adverse effects see eBNF for details
- GI upset (nausea, vomiting, constipation, anorexia/weight changes)

Important:
- SIADH; Rhabdomyolysis
- Neuroleptic malignant syndrome
- Withdrawal (particularly with venlafaxine) if treatment stopped abruptly – GI disturbance, anxiety, dizziness, paraesthesia, tremor, sleep disturbance, sweating

Contra-indications and cautions
- Caution in the elderly, patients with cardiac disease, hepatic or renal impairment, diabetes, history of epilepsy, personal or family history of mania, raised intraocular pressure, susceptibility to angle-closure glaucoma, history of bleeding disorders, those taking other medications that increase bleeding risk
- Avoid in pregnancy, conditions associated with high risk of cardiac arrhythmia and uncontrolled hypertension

Interactions
- NSAIDs (increased risk of bleeding)
- Warfarin (enhanced anticoagulant effect)
- Antiepileptics (SSRIs lower the seizure threshold)
- Dopaminergics (increased risk of hypertension and CNS excitation) – selegiline should not be started until 1 week after stopping venlafaxine, venlafaxine should not be started until 2 weeks after stopping selegiline

Therapeutic drug monitoring
Safety: Patients with heart disease should have their blood pressure monitored during treatment. If confusion or falls occur, check U+E for a serum sodium concentration (rule out hyponatraemia).

Efficacy: Depends on clinical indication e.g. improvement/resolution of symptoms of depression

Patient communication:
Explain to patients that this medication may impair their ability to perform skilled tasks such as driving and may cause drowsiness.

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Anti-Emetics

Mode of Action

**Dopamine antagonist anti-emetics e.g. Domperidone, Metoclopramide** are antagonists at dopamine D₂ receptors in the chemoreceptor trigger zone of the medulla oblongata. These drugs also have direct prokinetic effects on the GI tract, accelerating gastric emptying and intestinal transit.

**Antihistamine anti-emetics e.g. Cyclizine** are antagonists at histamine H₁ receptors in the chemoreceptor trigger zone (CTZ) of the medulla oblongata. This reduces transmission along neuronal pathways from the vestibular apparatus to the CTZ.

**5-Hydroxytryptamine anti-emetics e.g. Ondansetron** are highly selective antagonists at serotonin 5-HT₃ receptors present both centrally within the chemoreceptor trigger zone and peripherally within the GI tract. This directly inhibits serotonin activity within the area postrema and CTZ, while also preventing stimulation of the CTZ by visceral afferents.

**Clinical indications:**

- Nausea/vomiting including post-operative nausea/vomiting (PONV) and that associated with chemotherapy and radiotherapy
- Motion sickness

**Prescribing and Safety**

- **Domperidone:** 10mg up to 3 times daily
- **Metoclopramide:** 10mg 3 times daily
- **Cyclizine:** 50mg up to 3 times daily

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
**Ondansetron**: For emetogenic chemotherapy – 8mg 1 hour prior; For prevention of post-operative nausea/vomiting – 16mg 1 hour before anaesthesia; For treatment of PONV – 4mg IM or IV
Reduce dose or avoid in hepatic and renal impairment.

**Adverse effects:**
**Domperidone/Metoclopramide:**
- Drowsiness; extrapyramidal symptoms (especially in children and young adults)
- Hyperprolactinaemia
- Oculogyric crisis, QT prolongation (domperidone only)
**Ondansetron:**
- Common: Constipation, flushing, headache
- Less common but important: Hypotension, Bradycardia, movement disorders
**Cyclizine:**
- Drowsiness
- Antimuscarinic effects – dry mouth, blurred vision, urinary retention, constipation

**Contra-indications and cautions**
- Domperidone should be used at the lowest effective dose for the shortest possible duration (max. treatment duration should not normally exceed 1 week);
- Domperidone is contra-indicated for use in conditions where cardiac conduction is, or could be impaired, or where there is underlying cardiac disease, when administered concomitantly with drugs that prolong the QT interval or potent CYP3A4 inhibitors, and in severe hepatic impairment
- Caution in patients under 20 and the elderly, epilepsy and atopic allergy (including asthma)
- Avoid in GI obstruction, perforation or haemorrhage; avoid cyclizine in severe prostatic hypertrophy

**Interactions**
- **Avoid giving ondansetron or domperidone with other drugs that prolong the QT interval**
- Liver enzyme inducers e.g. phenytoin, carbamazepine (reduced anti-emetic effect of ondansetron)

**Therapeutic drug monitoring**

**Safety:** Monitor clinically for adverse effects

**Efficacy:** Improvement/resolution of symptoms

**Patient communication:** Advise patients taking cyclizine that this medication can cause drowsiness and may impair their ability to drive and operate machinery – if this happens they should avoid these activities until the effects wear off.

**Additional comments:** Always establish a cause for vomiting before prescribing an anti-emetic. Encourage adequate fluid intake to compensate for that lost while vomiting.
**Paracetamol**

**Drug Class:** Non-opioid analgesics, antipyretics; NB. Paracetamol is *not* an NSAID

**Other commonly used drugs in this class:**

**Mode of Action**

Is not fully understood, it likely involves:

**Target:** Cyclo-oxygenase (COX)3 enzyme in the CNS

**Action:** Central (not peripheral) inhibition

**Effect:** Inhibit synthesis of prostaglandins from arachidonic acid

**Overall effect:** peripherally blocks generation of pain impulses, reduces central pain signaling and inhibits the hypothalamic heat-regulation center

**Clinical indications:**

- Mild to moderate pain
- Pyrexia
Prescribing and Safety

0.5-1g every 4-6 hours, maximum 4g daily (maximum 3g daily in hepatocellular insufficiency)

Adverse effects

Side effects are rare but include:

Important:
- Blood disorders (thrombocytopenia, leucopenia, neutropenia)
- Hepatotoxicity in overdose (treat with N-acetyl-cysteine if indicated, see below)

Contra-indications and cautions

- Caution in alcohol dependence, chronic alcoholism, chronic malnutrition and dehydration

Interactions

- Hepatic enzyme inducers e.g. alcohol, antiepileptics (increased risk of hepatotoxicity in overdose – use lower threshold for treatment with N-acetyl-cysteine)

Therapeutic drug monitoring

Safety: In suspected/known overdose, paracetamol levels should be checked at least 4 hours after ingestion – treatment with N-acetyl-cysteine should be commenced within 8 hours of ingestion if levels exceed the treatment line on the paracetamol nomogram

Efficacy: Depends on indication – reduction in pain or temperature

Patient communication

Explain to patients that they must not take more than the recommended dose of paracetamol in a 24 hour period, which is 8 x 500mg tablets, or more than 2 x 500mg tablets at any one time, or any other paracetamol containing compound.

Additional comments

Paracetamol is the most commonly used drug in intentional overdose. The amount of drug ingested should be calculated relative to the patient’s weight:

- <150mg/kg unlikely to result in significant liver damage
- >250mg/kg significant risk of hepatocellular toxicity
- >12g potentially fatal

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**Codeine**

**Drug Class:** Weak opioids

**Other commonly used drugs in this class:** Dihydrocodeine

**Mode of Action**

**Target:** G-protein coupled opioid ‘mu’ receptors in the CNS and peripheral nervous system

**Action:** Partial agonist (weak affinity for receptors)

**Effect:** Closure of N-type voltage-dependent calcium channels and opening of calcium-dependent inwardly rectifying potassium channels

**Overall effect:** Membrane hyperpolarisation, preventing release of substance P and glutamate, blocking the pain signal and reducing neuronal excitability

**Clinical indications:**

- Mild to moderate pain
- Diarrhoea
- Cough suppression
Prescribing and Safety

30-60mg every 4 hours as required (maximum 240mg daily)

Adverse effects:
Common:
- Constipation, biliary/ureteric spasm, dysphoria, sweating
- Nausea/vomiting, drowsiness

Important:
- Respiratory depression (high doses)
- Hypotension (high doses)
- Paralytic ileus (dihydrocodeine)

Contra-indications and cautions
- Caution in the elderly, hypotension, shock, prostatic hypertrophy, obstructive ir inflammatory bowel disorders, biliary disease, convulsive disorders, adrenocortical insufficiency, hepatic or renal impairment and pregnancy
- Avoid in COPD, acute asthma attack, acute respiratory depression, comatose patients and those at risk of paralytic ileus

Interactions
- CNS depressants (increased risk of respiratory depression) – alcohol, sedatives, hypnotics, general anaesthetics

Therapeutic drug monitoring

Safety:

Efficacy: Depends on indication – improvement/resolution of pain, cough or diarrhoea

Patient communication:
Explain to patients that this medication could cause them to feel drowsy and that if this happens they should not drive or operate machinery. Patients should also be advised to avoid drinking alcohol while taking this medication.

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**Morphine**

**Drug Class:** Strong opioids

**Other commonly used drugs in this class:** Buprenorphine, diamorphine, fentanyl, methadone, oxycodone

**Mode of Action**

![Diagram of Morphine Mode of Action](image)

**Target:** G-protein coupled opioid ‘mu’ receptors in the CNS and peripheral nervous system

**Action:** Full agonist (high affinity for receptors)

**Effect:** Closure of N-type voltage-dependent calcium channels and opening of calcium-dependent inwardly rectifying potassium channels – this increases potassium conductance. Opioids also presynaptically inhibit the release of pain-signalling neurotransmitters such as substance P.

**Overall effect:** Membrane hyperpolarisation and reduced neuronal excitability, reduction or inhibition of pain neurotransmission.

**Clinical indications:**

- Moderate to severe pain (including use in palliative care)
- Acute diarrhoea (not first line)
- Cough in terminal care
Prescribing and Safety
Morphine: 10mg s/c or IM every 4 hours (5mg every 4 hours if elderly, reduce dose in hepatic or renal impairment), adjust according to response
Can also be administered by syringe driver or patient controlled analgesia (PCA) system.

Adverse effects: (see codeine)
Common:
- Constipation, biliary/ureteric spasm, dysphoria, sweating
- Nausea/vomiting, drowsiness

Important:
- Respiratory depression
- Hypotension
- Sedation and coma
- Tolerance
- Physical and psychological dependence
- Overdose – this is reversed with naloxone

Contra-indications and cautions
- Caution in the elderly, hypotension, shock, prostatic hypertrophy, obstructive or inflammatory bowel disorders, biliary disease, convulsive disorders, adrenocortical insufficiency, hepatic or renal impairment, pregnancy and patients with a history of drug dependence
- Avoid in acute respiratory depression, coma, head injury or raised ICP (opioids interfere with pupillary responses used in neurological assessment) and those at risk of paralytic ileus

Interactions
- CNS depressants (increased risk of respiratory depression) – alcohol, sedatives, hypnotics, general anaesthetics
- MAOIs (potentiate action of morphine)
- Alcohol (increased hypotensive and sedative effects)

Therapeutic drug monitoring
Safety: Monitor respiratory rate and oxygen saturation in hospitalised patients

Efficacy: Depends on indication – improvement/resolution of pain, cough or diarrhoea

Patient communication:
Explain to patients that this medication could cause them to feel drowsy and that if this happens they should not drive or operate machinery. Patients should also be advised to avoid drinking alcohol while taking this medication.
Carbamazepine

Drug Class: Antiepileptics

Other commonly used drugs in this class: oxcarbazepine

Mode of Action: unclear, thought to involve:

Target: Voltage-gated sodium channels

Action: Use-dependent blockade

Effect: Slows recovery of the voltage-gated sodium channels, opens potassium channels and promotes GABA release

Overall effect: Preferentially reduces excitability/blocks excitation of neurones that are firing repeatedly

Clinical indications:
- Epilepsy
- Trigeminal neuralgia
- Prophylaxis of bipolar disorder

Prescribing and Safety

Starting dose – 100-200mg 1-2 times daily (reduce if elderly); Maintenance dose 0.8-1.2g daily

Adverse effects:

Common:
- Allergic skin reactions; aplastic anaemia; ataxia; blood disorders; blurring of vision; dermatitis; dizziness; drowsiness; dry mouth; eosinophilia; fatigue; haemolytic anaemia; headache; hyponatraemia (leading in rare cases to water intoxication); leucopenia; nausea; oedema; thrombocytopenia; unsteadiness; urticaria; vomiting

Important:
- Cardiac conduction disturbances
- Leucopenia/bone marrow failure
- Stevens-Johnson syndrome (especially if Han Chinese or Thai origin due to HLA-B*1502 allele)

Contra-indications and cautions
- Caution in cardiac disease, hepatic or renal impairment, pregnancy, patients with history of haematological reaction to other drugs and those susceptible to angle-closure glaucoma
Avoid in patients with AV conduction abnormalities (if not paced), history of bone marrow depression, acute porphyria and those with known hypersensitivity to tricyclic antidepressants

Discontinue carbamazepine if patient develops acute liver disease or severe/progressive/symptomatic leucopenia

Interactions

- Warfarin (reduced anticoagulant effect)
- Antipsychotics (impaired anticonvulsant effect)
- CYP450 inhibitors (plasma levels increased) — includes isoniazid, diltiazem, verapamil
- CYP450 inducers (plasma levels reduced) — includes phenytoin, phenobarbitone, theophylline

Therapeutic drug monitoring

Safety: Monitor for symptomatic side effects, if confusion or falls occur, check U+E for a serum sodium concentration (rule out hyponatraemia)

Efficacy: Depends on indication — reduced seizure frequency or improvement/resolution of neuropathic pain

Patient communication:

Patients or their carers must be made aware of the signs of blood, liver or skin disorders and advised to seek immediate medical attention if these arise e.g. fever, rash, mouth ulcers, bruising, bleeding. Women of childbearing age should be given contraceptive advice. Although there is a risk of teratogenicity with antiepileptic medication, the risk of harm from convulsive seizures outweighs this. Folate supplementation prior to conception and in the first trimester of pregnancy is advised to prevent neural tube defects.

Additional information:

Preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, changing formulation should be avoided.

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**Pregabalin**

**Drug Class:** Antiepileptics

**Other commonly used drugs in this class:** Gabapentin

**Mode of Action**

Exact mechanism of action unclear. Although these drugs are GABA analogues, their clinical benefits are not thought to be mediated by action on GABA receptors in the CNS. It is thought to bind to the alpha2-delta protein an auxiliary subunit of the voltage-gated calcium channels. There are general reductions in a number of neurotransmitters being released with an overall neuroinhibitory action.

**Clinical indications:**

- Partial seizures with or without secondary generalisation
- Neuropathic pain
- Generalised anxiety disorders

**Prescribing and Safety**

Pregabalin:

Starting dose – 150mg daily in 2-3 divided doses

Maintenance dose – 300-600mg daily in 2-3 divided doses (reduce if elderly or renal impairment)

“Start low go slow” when increasing dose as sedation, confusion and ataxia have been reported with rapid titration

**Adverse effects:**

**Common:**

- Appetite changes; blurred vision; confusion; constipation; diplopia; disturbances in muscle control and movement; dizziness; drowsiness; dry mouth; euphoria; flatulence; impaired attention; impaired memory; insomnia; irritability; malaise; oedema; paraesthesia; sexual dysfunction; speech disorder; visual disturbances; visual field defects; vomiting; weight gain

**Important:**

- Hypertension
- Leucopenia

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Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Contra-indications and cautions
- Caution in the elderly, diabetes mellitus, renal impairment, severe congestive heart failure, pregnancy, breastfeeding and history of psychosis

Interactions
- Opiates (increased risk of CNS depression)
- Antacids containing aluminium and magnesium (reduced bioavailability of gabapentin)

Therapeutic drug monitoring
Safety:

Efficacy: Depends on indication – improvement/resolution of neuropathic pain, reduction in seizure frequency

Patient communication:
Patients should be advised that this medication may cause drowsiness and impair their ability to perform skilled tasks such as driving – if they do feel sleepy they should not drive or operate machinery.

Explain to patients that they should not take indigestion remedies 2 hours before or after taking their medication.

Advise patients that they should not stop taking this medication unless told to do so by their doctor.

Doctors should avoid abrupt withdrawal of pregabalin/gabapentin as this can cause anxiety, insomnia, pain and increased risk of seizures in epileptic patients.

Additional Information:
If used for neuropathic pain, discontinue treatment if sufficient benefit is not achieved within 8 weeks of reaching the maximum tolerated dose.
Lamotrigine

**Drug Class:** Antiepileptics

**Mode of Action**

**Target:** Voltage gated Na⁺ channels (selectively binds to the **inactivated** state of the channel)

**Action:** Inhibitor

**Effect:** Blocks repetitive firing of neurones by delaying membrane recovery

**Overall effect:** Stabilises presynaptic neuronal membrane, suppresses release of excitatory amino acid glutamate which plays a key role in the generation of seizures

**Clinical indications:**

- Simple and complex partial seizures
- Absence seizures
- Generalised tonic-clonic seizures

**Prescribing and Safety**

**Starting dose** – 25mg daily once daily for 14 days

**Maintenance dose** – 100-200mg daily in 1-2 divided doses

**Adverse effects:**

**Common:**
- Blurred vision; aggression; agitation; arthralgia; ataxia; back pain; diarrhoea; diplopia; dizziness; drowsiness; dry mouth; headache; insomnia; nausea; nystagmus; rash; tremor; vomiting

**Important:**
- Hypersensitivity syndrome including DIC and multi-organ dysfunction
- Bone marrow failure
- **Skin reactions** including Stevens-Johnson syndrome and toxic epidermal necrolysis

**Contra-indications and cautions**

- Caution in hepatic and renal impairment (reduce dose) and in patients with myoclonic seizures
- Avoid in pregnancy and patients with known hypersensitivity to lamotrigine
• Discontinue lamotrigine immediately if patient develops rash or serious skin reaction (otherwise avoid abrupt withdrawal)

**Interactions**
• Antidepressants (lower seizure threshold) – tricyclics, SSRIs, MAOIs, St. John’s Wort
• Oestrogens/OCP (plasma concentration of lamotrigine reduced) – lamotrigine dose adjustment often necessary
• Other antiepileptics (altered plasma concentration)

**Therapeutic drug monitoring**

**Safety:**

**Efficacy:** Reduced seizure frequency

**Patient communication:**

Explain to patients that they must not stop taking this medication unless told to do so by their doctor.

Patients must also be made aware of the symptoms and signs of hypersensitivity syndrome e.g. rash, fever, lymphadenopathy and advised to see their doctor immediately if any of these develop.

Patients and doctors should be alert for symptoms and signs of bone marrow failure e.g. anaemia, bruising, infection.

Patients should be informed that this medication carries a risk of suicidal thoughts/behaviours and that they must report any emergence or worsening of depression or related symptoms immediately. Advise patients that this medication can cause drowsiness and may affect their ability to drive and operate machinery.

**Additional comments:**

Medication errors have occurred with different preparations of lamotrigine – do not confuse the different combinations, preparations or indications of this medication when prescribing or dispensing lamotrigine. Patients may wish to visually inspect their tablets to verify that they are receiving lamotrigine and in the correct formulation.
Levetiracetam

Drug Class: Antiepileptics

Mode of Action

Precise mechanism of action not known but levetiracetam may block exocytosis of neurotransmitters and reduce intraneuronal calcium levels.

Clinical indications:

Focal (partial) seizures with or without secondary generalisation

Prescribing and Safety

Starting dose – 250mg once daily
Maintenance dose – 250-1.5g twice daily according to response (half in hepatic impairment, reduce in renal impairment according to eGFR)

Adverse effects:

Common:
- Abdominal pain; aggression; anorexia; anxiety; ataxia; convulsion; cough; depression; diarrhoea; dizziness; drowsiness; dyspepsia; headache; insomnia; irritability; malaise; nasopharyngitis; nausea; rash; tremor; vertigo; vomiting

Contra-indications and cautions
- Caution in hepatic and renal impairment
- Avoid in pregnancy and breastfeeding unless benefit outweighs risk

Interactions
- Antidepressants (lower seizure threshold) – tricyclics, SSRIs, MAOIs, St. John’s Wort

Therapeutic drug monitoring

Safety:

Efficacy: Reduction in seizure frequency

Patient communication:

Explain to patients that they should not stop taking this medication unless told to do so by their doctor.

Advise patients that this medication can cause mild drowsiness and could affect their ability to drive and operate machinery.

Additional information: Levetiracetam should not be withdrawn abruptly.
Phenytoin

Drug Class: Antiepileptics

Mode of Action

Target: Voltage-gated neuronal sodium ion channels

Action: Block

Effect: Inhibits influx of sodium ion into neuronal cells/slows rate of recovery of sodium channels from inactivation

Overall effect: Stabilises the neuronal membrane and prevents hyperexcitability, thus limiting the spread of seizure activity and reducing seizure propagation

Clinical indications:

- All forms of epilepsy except absense seizures
- Status epilepticus

Prescribing and Safety

Starting dose – 3-4mg/kg or 150-300mg daily, increased gradually as necessary while monitoring plasma phenytoin concentration

Maintenance dose – 200-500mg daily (reduce in hepatic impairment to avoid toxicity)

Adverse effects:

P = P450 interactions
H = Hirsutism
E = Enlarged gums
N = Nystagmus
Y = Yellow-browning of the skin
T = Teratogenic
O = Osteomalacia
I = Interferes with folate metabolism, leads to anaemia
N = Neuropathies: vertigo, ataxia, headaches

Contra-indications and cautions

- Caution in patients undergoing enteral feeding
- Avoid in patients of Han Chinese or Thai origin (HLA-B*1502 allele increases risk of Stevens-Johnson syndrome)
- Discontinue phenytoin if severe leucopenia develops
Interactions
Phenytoin is a cytochrome P450 Inducer

- OCP (reduced contraceptive effect)
- Theophylline (reduced plasma concentration of both drugs)
- Cimetidine (reduced plasma phenytoin concentration)
- Amiodarone (increased plasma phenytoin concentration)

Therapeutic drug monitoring

Safety: Phenytoin has a narrow therapeutic index and relationship between dose and plasma concentration is not linear – small dosage increases in some patients may produce large increases in plasma concentration. It is therefore important to monitor plasma phenytoin concentration to improve dosage adjustment and ensure dose is within therapeutic range (10-20mg/l).

Efficacy: Reduction in frequency of seizures

Patient communication:
Patients or their carers should be told how to recognise signs of blood or skin disorders and advised to seek immediate medical attention if any of the following develop: fever, rash, mouth ulcers, bruising, bleeding.

Advise patients to take this medicine with or after food.

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**Sodium Valproate**

**Drug Class:** Antiepileptics

**Mode of Action**

**Target:** Voltage-gated sodium channels

**Action:** Inhibitor

**Effect:** Inhibit inactivation of inhibitory neurotransmitter GABA and block its reuptake into neurones

**Overall effect:** Inhibition of action potential transmission both pre- and post-synaptically, leading to increased levels of GABA in the brain and interruption of seizure activity

**Clinical indications:**

Epilepsy – all forms

**Prescribing and Safety**

Starting dose – 600mg daily in 1-2 divided doses, increase by 200mg every 3 days
Maintence dose – 1-2g daily (reduce in renal impairment)

**Adverse effects:**

**Common:**

- Aggression; anaemia; confusion; convulsion; deafness; diarrhoea; extrapyramidal disorders; gastric irritation; haemorrhage; headache; hyponatraemia; memory impairment; menstrual disturbance; nausea; nystagmus; somnolence; stupor; thrombocytopenia; transient hair loss (regrowth may be curly); tremor; weight gain

**Important:**

- Thrombocytopenia
- Pancreatitis
- Hyperammonaemia
- Reduced bone mineral density
- Hepatic dysfunction (including fatal hepatic failure)

**Contra-indications and cautions**

- Caution in renal impairment and systemic lupus erythematosus
- Avoid in active liver disease, hepatic impairment, pregnancy and in patients with family history of severe hepatic dysfunction
- Discontinue if patient develops abnormally prolonged prothrombin time, pancreatitis, blood disorder or hepatic dysfunction
Interactions
- Antidepressants (reduced anticonvulsant effect) – SSRIs, TCAs, MAOIs
- Antimalarials (reduced anticonvulsant effect) – mefloquine, chloroquine

Therapeutic drug monitoring
**Safety:** Check FBC prior to commencing treatment and before surgical procedures, LFTs should be checked at baseline and every 6 months during treatment

**Efficacy:** Reduced seizure frequency; serum valproate levels can be used to monitor compliance

**Patient communication:**
Patients or their carers should be told how to recognise signs and symptoms of blood and liver disorders and advised to seek immediate medical attention if these develop. Patients or their carers should also be advised to see immediate attention if symptoms of pancreatitis (severe epigastric pain radiating to the back, nausea, vomiting) develop.

Female patients of childbearing age should be made aware of the need for reliable contraception during treatment as this medication can pose risks during pregnancy. If the patient does wish to become pregnant they should seek specialist advice.

NB. Sodium valproate may cause a false positive result on urinary ketone testing.

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**Co-Beneldopa**

**Drug Class:** Dopamine receptor agonists

**Other commonly used drugs in this class:** Co-Careldopa

The active ingredient in Co-Beneldopa and Co-Careldopa is Levodopa, the metabolic precursor to dopamine. Each also contains an extracerebral dopa-decarboxylase inhibitor to reduce peripheral conversion of levodopa to dopamine before it crosses the blood-brain barrier. This limits side effects such as nausea, vomiting and cardiovascular effects.

**Mode of Action**

**Target:** Dopamine receptors in the striatum, pallidum and substantia nigra

**Action:** Agonist

**Effect:** Enhanced dopaminergic transmission through exogenous supplementation of dopamine

**Overall effect:** Restore normal levels of dopamine

**Clinical indications:**

Parkinson’s disease

**Prescribing and Safety**

Starting dose – 50mg 3-4 times daily (1-2 times daily if elderly)

Maintenance dose – 400-800mg daily in divided doses

**Adverse effects**

**Common:** Abnormal dreams; anorexia; anxiety; arrhythmias; chorea; confusion; dementia; depression; dizziness; drowsiness; dry mouth; dyskinesia; dystonia; euphoria; fatigue; insomnia; nausea; palpitations; postural hypotension; psychosis; syncope; taste disturbances; vomiting

**Important:**

- Dyskinesia (seen in majority of patients within 2 years of commencing levodopa)

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
• Rapid fluctuations in clinical state – “on-off effect” (reduce drug dose, increase frequency)

• Psychological effects including dementia, depression and schizophrenia-like syndrome with delusions and hallucinations

• Postural hypotension

**Contra-indications and cautions**

• Caution in severe pulmonary or cardiovascular disease, psychiatric illness (avoid if severe), endocrine disorders including diabetes mellitus, pregnancy, patients with history of convulsions or peptic ulcer disease, susceptibility to angle-closure glaucoma and in those with hepatic or renal impairment

• Avoid in breastfeeding

• Discontinue if patient develops deterioration in existing psychiatric illness

**Interactions**

• **MAOIs** (risk of hypertensive crisis – do not start levodopa until at least 2 weeks after stopping MAOIs)

• Antihypertensives (increased hypotensive effect)

**Therapeutic drug monitoring**

**Safety:** Monitor blood pressure at baseline and during treatment due to risk of postural hypotension

**Efficacy:** Improvement in symptoms

**Patient communication**

Warn patients to be cautious when driving or operating machinery as this medication may cause drowsiness. If they do start to experience excessive sedation or sudden onset of sleep they must not drive or operate machinery until this stops happening.

Patients should be advised not to stop taking their medication suddenly as this can lead to neuroleptic malignant syndrome and rhabdomyolysis. If it is necessary to withdraw this medication, doctors should do this slowly. Make patients aware of the symptoms of rhabdomyolysis (muscle pain, cramps, spasms or stiffness) and advise them to seek urgent medical attention if any of these develop.

Tell patients that this medication could cause their urine, saliva or sweat to turn a dark colour which may cause discolouration of clothing – this is normal and nothing to worry about.

Patients should be told to take their medicines at the same time each day.
Memantine

Drug Class: NMDA receptor antagonist

Other commonly used drugs in this class: None

Mode of Action

Target: NMDA receptor

Action: Non-competitive antagonist

Effect: Inhibits the prolonged continuous influx of calcium ions caused by high levels of excitatory amino acid glutamate in the brain of demented patients i.e. memantine protects against neuronal excitotoxicity induced by pathologically elevated glutamate levels

Overall effect: May slow deterioration in cognitive decline caused by Alzheimer’s disease

Clinical indications:

Alzheimer’s disease in patients with Mini Mental State Examination (MMSE) 10-20/30.

Prescribing and Safety

Starting dose – 5mg daily
Maintenance dose – 10mg twice daily

Adverse effects:

Common:

• Constipation; dizziness; drowsiness, confusion, headache and hypertension

Important:

• Thrombosis e.g. DVT; Heart failure

Contra-indications and cautions

• Caution in cardiac disease, renal impairment and patients with history of convulsions
• Avoid in severe hepatic impairment

Interactions

• Amantadine (increased risk of CNS toxicity)
• Ketamine (increased risk of CNS toxicity)

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
**Therapeutic drug monitoring**

**Safety:**

**Efficacy:** Patients should be assessed every 6 months using the MMSE – treatment should continue only if score remains above 10 and the drug is felt to have a worthwhile effect on the global, functional and behavioural condition of the patient.

**Patient communication:**
Advise patients or their carers that this medication should be **swallowed whole** with water and taken at around the **same time** each day. Patients should **not stop** taking memantine unless told to do so by their doctor.

Explain to patients or their carers that this medication can cause **drowsiness** and may impair ability to drive and operate machinery.

**Additional comments:**
Patient must have a formal diagnosis of Alzheimer’s disease made in a specialist clinic. The patient’s cognitive, global and behavioural functioning should be assessed along with likelihood of compliance with treatment.

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Infections

Amoxicillin

Drug Class: β-lactam antibiotics – Penicillins

Other commonly used drugs in this class: Ampicillin, Benzylpenicillin, Flucloxacillin, Phenoxymethylpenicillin, Piperacillin

Mode of Action

![Bacterial Cell Wall Diagram]

**Target:** Bacterial penicillin-binding proteins/transpeptidase enzymes

**Action:** Inhibitor

**Effect:** Inhibit cross-linking of NAMA/NAG peptide chains in the peptidoglycan bacterial cell wall

**Overall effect:** Weakening of bacterial cell wall leading to lysis (bacteriocidal)

**Clinical indications:**

- Amoxicillin, ampicillin – broad spectrum – respiratory infections, UTI, otitis media
- Benzylpenicillin – bacterial meningitis
- Flucloxacillin – cellulitis
- Piperacillin – extended spectrum – severe infection, pseudomonas

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Amoxicillin – 500mg every 8 hours
Benzylpenicillin – 2.4-4.8g daily in 4 divided doses (IM or slow IV injection)
Flucloxacillin – 250-500mg every 6 hours
Piperacillin (with tazobactam) – 2.25-4.5g every 6-8 hours (IV)

Adverse effects:

Important:
- Hypersensitivity reactions – skin rash, fever, anaphylaxis
- Antibiotic associated diarrhoea (oral penicillin)
- Encephalopathy due to cerebral irritation (high doses)
- Maculopapular rash when amoxicillin given to patients with glandular fever – avoid giving as ‘blind’ treatment of sore throat

Contra-indications and cautions
- Avoid in patients with known hypersensitivity reaction to penicillins or other beta lactam antibiotics

Interactions
- Warfarin (INR may be affected by broad spectrum penicillins)
- Methotrexate (increased risk of toxicity)

Therapeutic drug monitoring
Safety: Monitor clinically for adverse effects

Efficacy: Resolution of infection

Patient communication:
Explain to patients the importance of completing the full course of antibiotics as opposed to stopping their medication when they start to feel better.
Flucloxacillin should be taken on an empty stomach.

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Cefalexin

**Drug Class:** β-lactam antibiotics – Cephalosporins

**Other commonly used drugs in this class:** Cefixime, Cefotaxime, Ceftriaxone, Cefuroxime

**Mode of Action**

![Bacterial Cell Wall](image)

**Target:** Bacterial penicillin-binding proteins/transpeptidase enzymes

**Action:** Inhibitor

**Effect:** Inhibit cross-linking of NAMA/NAG peptide chains in the peptidoglycan bacterial cell wall

**Overall effect:** Weakening of bacterial cell wall leading to lysis (bacteriocidal)

**Clinical indications:**

- Meningitis and septicaemia (cefotaxime or ceftriaxone)
- Biliary tract infections
- Pneumonia, respiratory tract infections
Prescribing and Safety

Cefalexin: 250mg every 6 hours (1-1.5g every 6-8 hours in severe infection)

NB. Cefotaxime and ceftriaxone can only be given parenterally

Reduce dose/increase dosage interval in renal impairment.

Adverse effects

Common:
- Nausea/vomiting

Important:
- Hypersensitivity reactions including anaphylaxis (10% cross-sensitivity with penicillins)
- Antibiotic-associated diarrhoea/colicitis
- Cholestatic jaundice (ceftriaxone)
- Stevens-Johnson syndrome, toxic epidermal necrolysis

Contra-indications and cautions

- Caution in renal impairment
- Avoid in patients with known hypersensitivity reaction to cephalosporins or other beta-lactams

Interactions

- Aminoglycoside antibiotics (increased risk of nephrotoxicity)
- Oral contraceptive pill (reduced efficacy of OCP)

Therapeutic drug monitoring

Efficacy: Resolution of infection

Patient communication

Explain to patients the importance of completing the full course of antibiotics as opposed to stopping their medication when they start to feel better.

Female patients should be advised to use alternative methods of contraception whilst on this antibiotic.

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**Meropenem**

**Drug Class:** β-lactam antibiotics – Carbapenems

**Other commonly used drugs in this class:** Doripenem, Ertapenem, Imipenem

**Mode of Action**

![Diagram of Bacterial Cell Wall and Key]

**Target:** Bacterial penicillin-binding proteins/transpeptidase enzymes

**Action:** Inhibitor

**Effect:** Inhibit cross-linking of NAMA/NAG peptide chains in the peptidoglycan bacterial cell wall

**Overall effect:** Weakening of bacterial cell wall leading to lysis (bacteriocidal)

**Clinical indications:**

Carbapenems have a broad spectrum of activity against both aerobic and anaerobic gram +ve and gram -ve bacteria.

- *Pseudomonas aeruginosa* infection
- Community and hospital acquired pneumonia
- Intra-abdominal infections
- Complicated urinary tract infections
Prescribing and Safety

Carbapenems are given by intravenous infusion.

Meropenem: 0.5-1g every 8 hours
Imipenem: 1-2g daily in 3-4 divided doses
Ertapenem: 1g once daily
Doripenem: 500mg every 8 hours

Adverse effects:

Common:
- Abdominal pain; diarrhoea; disturbances in liver function tests; headache; nausea; pruritus; thrombocythaemia; vomiting

Important:
- Hypersensitivity reactions – skin rash, fever, anaphylaxis
- Antibiotic associated colitis
- Neurotoxicity including seizures, especially with high dose/renal failure/CNS disease

Contra-indications and cautions
- Caution in the elderly, renal impairment and those with CNS disorders e.g. epilepsy
- Avoid in pregnancy, breastfeeding and in patients with known hypersensitivity reaction to carbapenems or other beta lactam antibiotics

Interactions
- Antiepileptics – sodium valproate (reduced plasma valproate concentration, possible therapeutic failure)

Therapeutic drug monitoring
Safety: Monitor clinically for adverse effects, particularly in patients at risk of neurotoxicity

Efficacy: Resolution of infection

Additional information:
Imipenem is partially inactivated by enzymes in the kidney – to avoid this it should be given with enzyme inhibitor Cilastatin. This does not apply to the other carbapenems.
**Doxycycline**

**Drug Class:** Tetracycline antibiotics

**Other commonly used drugs in this class:** *Lyme cycline, Minocycline, Tetracycline*

**Mode of Action**

**Target:** Bacterial 30s ribosomal subunit

**Action:** Reversibly binds to the 30s ribosomal subunit blocking tRNA binding

**Effect:** Inhibit aminoacyl tRNA and mRNA ribosomal complex formation therefore inhibit bacterial protein synthesis

**Overall effect:** Bacteriostatic effect

**Clinical indications:**

Usefulness of tetracyclines has declined due to the development of resistance, however some uses include:

- Infections caused by chlamydia, rikettsia, brucella and *borrelia burgdorferi* (causes Lyme disease)
- Mixed respiratory tract infection e.g. exacerbation of chronic bronchitis
- Acne vulgaris, acne rosacea
- Alternative in community acquired pneumonia e.g. in patients who are allergic to other antibiotics

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Doxycycline: 100mg 1-2 times daily (depending on indication the duration of treatment may vary – see BNF)

Adverse effects

Common:
- GI disturbance
- Dysphagia, oesophageal irritation

Important:
- Tooth staining, dental hypoplasia – ‘tetracycline teeth’ (tetracyclines chelate calcium and are deposited in growing bones and teeth, avoid in children and pregnant/breastfeeding women)
- Hepatotoxicity (particularly in pregnancy)
- Blood disorders

Contra-indications and cautions

- Caution in hepatic impairment
- Avoid in pregnant or breastfeeding women, children under 12 years and in patients with renal impairment

Interactions

- Warfarin (increased anticoagulant effect)
- Retinoids (increased risk of benign intracranial hypertension – do not co-prescribe)
- Ciclosporin (increased plasma ciclosporin concentration)
- Antacids and dairy products reduce the absorption of tetracyclines

Therapeutic drug monitoring

Safety:

Efficacy: Resolution of infection

Patient communication

Explain to patients the importance of completing the full course of antibiotics as opposed to stopping their medication when they start to feel better. Advise patients not to take indigestion remedies or milk at the same time of day as this medicine.

Patients taking tetracycline should be advised to take their medication with plenty of water while sitting or standing. Those taking doxycycline should be advised to wear high-factor sunscreen and avoid direct sun exposure due to the risk of photosensitivity.
**Gentamicin**

**Drug Class:** Aminoglycoside antibiotics

**Other commonly used drugs in this class:** Neomycin, Tobra mycin

**Mode of Action**

**Target:** Bacterial 30s ribosomal subunit

**Action:** Inhibits normal ribosomal functioning in 3 ways:

**Effect:** Interfere with the initiation complex of peptide formation, induce misreading of mRNA, break up ribosomal clusters (polysomes)

**Overall effect:** Block bacterial protein synthesis leading to cell death (bacteriocidal)

NB. Aminoglycosides require oxygen-dependent transport to enter the bacterial cell and are therefore ineffective against anaerobes.

**Clinical indications:**

Effective against aerobic gram +ve and some gram –ve bacteria
- Meningitis and septicaemia
- Biliary tract infection
- Acute pyelonephritis
- Endocarditis in combination with other antibiotics
- *Pseudomonas aeruginosa* infection (Tobramycin)
Prescribing and Safety
Aminoglycoside antibiotics must be given parenterally (IV or IM) as they are not well absorbed from the gut. Loading and maintenance doses can be calculated on the basis of a patient’s weight and renal function using a nomogram.

Gentamicin: either 3-5mg/kg daily in divided doses every 8 hours or 5-7mg/kg once daily

Tobramycin: 3-5mg/kg daily in divided doses every 8 hours

Reduce dose and increase dosage interval in renal impairment. Do not use once daily dosage regimen if creatinine clearance <20ml/minute.

To avoid excessive dosage in obese patients, use ideal weight for height to calculate dose and then monitor serum aminoglycoside concentrations closely.

Adverse effects

Important:

- Nephrotoxicity (usually reversible when drug stopped)
- Ototoxicity (usually irreversible) (rare before 2 weeks of treatment)

Contra-indications and cautions

- Caution in renal impairment and extremes of age
- Avoid in pregnancy and in patients with myasthenia gravis

Interactions

- Loop diuretics e.g. Furosemide (increased risk of ototoxicity – do not co-prescribe)
- Vancomycin (increased risk of ototoxicity)
- NSAIDs (increased risk of nephrotoxicity)

Therapeutic drug monitoring

Safety: Renal function should be measured at baseline, re-check U+E regularly during treatment; ask patient to report any changes in hearing or balance to detect ototoxicity

Serum aminoglycoside levels should be checked regularly – scheduling of monitoring varies depending on single-dose or multiple dose regimens. Blood samples should be taken 1 hour after IV or IM administration (peak concentration) and just before the next dose (trough concentration).

If peak is high, reduce dose. If trough is high, increase dosage interval (+/- reduce dose).

Efficacy: Resolution of infection
Additional information:

Once daily dosing regimens are preferable as they are more easily adhered to and provide adequate serum aminoglycoside concentrations.

Adverse effects of aminoglycosides are dose related and, where possible, treatment should last no longer than 7 days.

Aminoglycosides work synergistically with agents that interfere with cell wall synthesis e.g. β lactams, vancomycin.
Clarithromycin

Drug Class: Macrolide antibiotics

Other commonly used drugs in this class: Azithromycin, Erythromycin

Mode of Action

Target: 50s subunit of bacterial ribosome

Action: Reversibly bind

Effect: Prevent transfer of bacterial tRNA from A-site to P-site on the ribosome, thus preventing elongation of the polypeptide chain (bacteriostatic)

Overall effect: Inhibit bacterial protein synthesis

Clinical indications:

Macrolides have a broad spectrum of action against gram positive and some gram negative bacteria e.g. Chlamydia trachomatis

- Lower respiratory tract infections (alone or in combination)
- Bacterial upper respiratory tract infections
- Mild-moderate soft tissue infections such as cellulitis
- As part a drug combination for H. pylori eradication
- Chlamydia trachomatis (eye and genital infections)
Prescribing and Safety

Acute infections – 500mg every 12 hours

Adverse effects:

Common:
- GI upset (nausea, vomiting, abdominal discomfort, diarrhoea)
- Taste/smell disturbance

Important:
- QT interval prolongation, arrhythmias
- Hepatotoxicity
- Stevens-Johnson syndrome, toxic epidermal necrolysis

Contra-indications and cautions
- Caution in hepatic and renal impairment (avoid if severe) and in patients with predisposition to QT interval prolongation

Interactions
- Theophylline (increased plasma theophylline concentration, risk of toxicity)
- Warfarin (increased anticoagulant effect)
- Antipsychotics – risk of ventricular arrhythmias
- Colchicine – increased risk of toxicity, suspend or reduce colchicine dose
- Statins – increased risk of myopathy; if myalgia occurs stop the statin and check CK level for signs of muscle breakdown, also check U+E

Therapeutic drug monitoring

Safety: Check ECG QT interval if any cardiac symptoms

Efficacy: Resolution of infection

Patient communication:
Explain to patients the importance of completing the full course of antibiotics as opposed to stopping their medication when they start to feel better.
**Vancomycin**

**Drug Class:** Glycopeptide antibiotics

**Other commonly used drugs in this class:** Teicoplanin

**Mode of Action**

**Target:** Terminal moieties of the NAMA and NAG peptides

**Action:** Binding

**Effect:** Irreversibly block the elongation of peptidoglycan chains by preventing the incorporation of NAMA and NAG peptide subunits

**Overall effect:** Inhibit bacterial cell wall synthesis leading to cell death (bactericidal)

**Clinical indications:**

Glycopeptides are active against aerobic and anaerobic gram +ve bacteria. They are unable to penetrate the cell membrane of gram -ve bacteria due to their high molecular weight.

- Gram positive infections including MRSA
- Antibiotic associated colitis caused by C. Difficile
- Endocarditis

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Vancomycin: for systemic infection 1-1.5g intravenously every 12 hours (half dose in elderly); for C. difficile infection 125mg orally every 6 hours for 10-14 days

Teicoplanin: If patient <70kg give 400mg every 12 hours for 3 doses then once daily; if patient >70kg give 6mg/kg every 12 hours for 3 doses the once daily

Adverse effects

Common:
- Nausea/vomiting

Important:
- Nephrotoxicity
- Ototoxicity (discontinue vancomycin if tinnitus occurs)
- Blood disorders – neutropenia, thrombocytopenia, agranulocytosis
- Severe hypotension, anaphylactoid reaction on rapid infusion

Contra-indications and cautions

- Caution in the elderly and in renal impairment
- Avoid in patients with history of deafness

Interactions

- Aminoglycosides (increased risk of nephrotoxicity and ototoxicity)
- Loop diuretics (increased risk of toxicity)

Therapeutic drug monitoring

Safety: Monitor blood counts, urinalysis and renal function (U+E, eGFR) daily in all patients taking vancomycin. Teicoplanin does not require routine monitoring unless patient has renal impairment.

All patients on vancomycin require plasma-vancomycin measurement – trough levels should be checked before the third or fourth dose after starting treatment or changing dose.

Efficacy: Resolution of infection

Additional information:

Avoid rapid infusion rates with IV vancomycin as this can precipitate anaphylactoid reactions and 'red man syndrome' (due to histamine release). Rotate IV sites to minimise local irritation.
**Trimethoprim**

**Mode of Action**

![Diagram of Trimethoprim mode of action]

**Target:** Bacterial dihydrofolate reductase

**Action:** Inhibitor

**Effect:** Inhibits reduction of dihydrofolate acid (DHF) to tetrahydrofolic acid (THF), an essential precursor in the thymidine synthesis pathway – interference with this pathway inhibits bacterial DNA synthesis

**Overall effect:** Limits bacterial reproduction

**Clinical indications:**

Simple UTI

As co-trimoxazole – *Pneumocystis carinii* pneumonia in AIDS patients

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Acute infections – 200mg every 12 hours, half dose in renal impairment
Prophylaxis – 100mg nocte

Adverse effects:
Common:
• GI disturbance (nausea, vomiting)

Important:
• Hyperkalaemia
• Hypersensitivity reactions – erythema multiforme, toxic epidermal necrolysis, angioedema, anaphylaxis
• Depression of haematopoeisis

Contra-indications and cautions
• Caution in patients with predisposition to folate deficiency, acute porphyria, renal impairment, neonates and the elderly
• Avoid in patients with blood dyscrasias and in pregnancy

Interactions
• ACE inhibitors, ARBs (risk of hyperkalaemia)
• Amiodarone (risk of ventricular arrhythmias)
• Phenytoin
• Azathioprine (increased risk of haematological toxicity)
• Methotrexate, mercaptopurine (increased risk of haematological toxicity)

Therapeutic drug monitoring
Safety: FBP should be monitored in patients on long term treatment due to the risk of blood disorders

Efficacy: Resolution of infection

Patient communication:
Explain to patients the importance of completing the full course of antibiotics as opposed to stopping their medication when they start to feel better.

Patients on long-term treatment (and their carers) should be told how to recognise the signs of blood disorders and advised to seek immediate medical attention if any of the following develop: fever, sore throat, rash, mouth ulcers, purpura, bruising, bleeding.

Maintain adequate fluid intake

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Metronidazole

Drug Class:

Other commonly used drugs in this class: Tinidazole

Mode of Action

The precise mechanism of action of metronidazole is not clear. However, it possesses a nitro-group which becomes charged and trapped within the intracellular compartment of anaerobic organisms leading to bacterial DNA damage and cell death.

Clinical indications:

- Anaerobic infections – first line in C. difficile colitis
- Abdominal sepsis
- Protozoal infections
- Dental infections
Prescribing and Safety
For anaerobic infections - either 800mg initially then 400mg every 8 hours or 500mg every 8 hours

Adverse effects

Common:
- GI disturbance
- Metallic taste
- Dizziness, headache

Important:
- Rarely – hepatitis, pancreatitis, peripheral neuropathy

Contra-indications and cautions
- Caution in pregnancy, breastfeeding and hepatic impairment (reduce dose)

Interactions
- **Alcohol – disulfiram-like reaction (AVOID)
- Warfarin (increased anticoagulant effect)
- Acitretin (increased risk of hepatotoxicity – avoid concomitant use)
- Clozapine (increased risk of agranulocytosis – avoid concomitant use)

Therapeutic drug monitoring

Safety: Clinical and laboratory monitoring advised if treatment exceeds 10 days

Efficacy: Resolution of infection

Patient communication

Explain to patients the importance of completing the full course of antibiotics as opposed to stopping their medication when they start to feel better.

Patients must AVOID ALCOHOL while taking metronidazole and for 48 hours after stopping.
Ciprofloxacin

**Drug Class:** Quinolone antibiotics

**Other commonly used drugs in this class:** Levo*fl*oxacin, Moxifo*loxacin, Ofo*loxacin

**Mode of Action**

![Diagram of Ciprofloxacin mode of action](image)

**Target:** Bacterial DNA gyrase (topoisomerase II)

**Action:** Inhibitor

**Effect:** Inhibit supercoiling of the bacterial DNA double helix

**Overall effect:** Prevent bacterial DNA replication, transcription, repair and recombination

**Clinical indications:**

Quinolones are active against gram –ve and gram +ve bacteria, particularly gram –ve enteric coliforms.

- Urinary tract infection
- Lower respiratory tract infection including community acquired pneumonia
- Gastrointestinal infections including typhoid fever
- Prostatitis

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety
Ciprofloxacin, levofloxacin: 500mg twice daily
Moxifloxacin, ofloxacin: 200-400mg once daily

Adverse effects

Common:

- GI disturbance e.g. nausea, vomiting, dyspepsia, diarrhoea – risk of C. Difficile
- Headache

Important:

- Tendon damage and rupture
- Depression, anxiety, psychoses, convulsions

Contra-indications and cautions

- Caution in epilepsy, G6PD deficiency, children/adolescents and in those with history of psychiatric illness
- Avoid in pregnancy, patients with known hypersensitivity to quinolones and in those with history of tendon disorders related to quinolone use
- Discontinue if patient develops psychiatric, neurological or hypersensitivity reactions or if tendinitis is suspected

Interactions

- NSAIDs (increased risk of convulsions)
- Theophylline (increased risk of convulsions, increased plasma theophylline concentration)
- Warfarin (increased anticoagulant effect)
- Antipsychotics (increased risk of ventricular arrhythmias)

Therapeutic drug monitoring
Safety: Monitor clinically for adverse effects

Efficacy: Resolution of infection

Patient communication:

Advise patients to drink plenty of fluids while on this medication. Patients should avoid taking indigestion remedies at the same time of day as this antibiotic.

Explain to patients the importance of completing the full course of antibiotics as opposed to stopping their medication when they start to feel better.

Explain that this medication may affect ability to drive and operate machinery, and that it enhances the effects of alcohol.
Nitrofurantoin

Drug Class: Nitrofuran antibiotics

Other commonly used drugs in this class:

Mode of Action: Poorly understood.

It is thought to inhibit a number of bacterial enzymes including those involved in bacterial carbohydrate metabolism and those involved in cell wall synthesis.

Prescribing and Safety

50mg every 6 hours with food for 7 days (100mg if chronic recurrent infection)

Adverse effects

Common:

- GI disturbance (nausea, vomiting, diarrhoea)

Important:

- Peripheral neuropathy
- Pulmonary fibrosis
- Hypersensitivity reactions involving skin and bone marrow
- Haemolytic anaemia

Contra-indications and cautions

- Caution in anaemia, diabetes mellitus, vitamin B12 and folate deficiency, pulmonary disease, hepatic and renal impairment and any condition associated with peripheral neuropathy (severe and irreversible neuronal damage may result)
- Avoid in pregnant women at term, breastfeeding, acute porphyria, those with G6PD deficiency and infants under 3 months
- Discontinue nitrofurantoin if patient suffers deterioration in lung function

Therapeutic drug monitoring

Efficacy: Resolution of infection

Patient communication

Explain to patients that they must complete the full course of antibiotics as opposed to stopping when they start to feel better. Also inform patients that the medication may cause their urine to turn a brown colour – this is normal and nothing to worry about. Patients should be advised to take
this medication with food (a small amount is sufficient) and to swallow the tablets whole without chewing.

**Additional comments**

For females with uncomplicated UTI a 3 day course is usually sufficient. If there is a chance of bacteraemia, Nitrofurantoin should not be used as its concentration in plasma is low.

Use with caution and only for 3-7 days if eGFR 30-44mL/min, may be less effective at treating UTI if renal impairment.

NB. Nitrofurantoin is ineffective against *proteus* and *pseudomonas* UTIs.
**Fluconazole**

**Drug Class:** Triazole antifungals

**Other commonly used drugs in this class:** Itraconazole

**Mode of Action**

**Target:** Fungal cytochrome P450 3A enzyme (responsible for converting lanosterol to ergosterol)

**Action:** Inhibitor

**Effect:** Depletion of ergosterol, a key component of the fungal cell membrane – this alters the fluidity of the membrane and thus interferes with membrane-associated enzymes

**Overall effect:** Inhibition of fungal cell replication

**Clinical indications:**
- Candidal infections including vaginal and mucosal candidiasis and candidaemia
- Prevention of fungal infections in immunocompromised patients
- Dermatological fungal infections e.g. tinea pedis, pityriasis versicolor
- Systemic fungal infections including histoplasmosis, cryptococcosis, etc.

**Prescribing and Safety**

Fluconazole: dose varies according to indication, in general – 50mg daily (200-400mg in severe or invasive infection)

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Itraconazole: 100-200mg daily

**Adverse effects**

**Common:**
- GI disturbance e.g. nausea, diarrhoea, rash and headache

**Important:**
- Hepatotoxicity (especially with itraconazole)
- Paraesthesia, peripheral neuropathy (itraconazole)
- Toxic epidermal necrolysis, Stevens-Johnson syndrome (more likely in AIDS patients)

**Contra-indications and cautions**
- Caution in renal and hepatic impairment (avoid if risk of toxicity outweighs potential benefit) and in those susceptible to congestive heart failure
- Avoid in pregnancy and active liver disease
- Discontinue if patient develops signs or symptoms of hepatic disease

**Interactions**
- Calcium channel blockers – negative inotropic effect, can precipitate heart failure
- Warfarin (increased anticoagulant effect)
- Sulphonylureas (increased plasma sulphonylurea concentration)
- Colchicine (increased risk of colchicine toxicity – hold/reduce dose of colchicine while patient is taking a triazole antifungal)
- Statins (increased risk of myopathy)

**Therapeutic drug monitoring**

**Safety:** Monitor LFT if giving a high dose, if treatment continues for more than one month, if patient is receiving other hepatotoxic drugs, if patient has history of hepatotoxicity with other drugs or if patient has pre-existing hepatic impairment

**Efficacy:** Resolution of infection

**Patient communication:**

Female patients taking Itraconazole should be advised to use reliable contraception during treatment and until their next menstrual period following the end of treatment. Explain to patients that they should complete the full prescribed course of their medication as opposed to stopping when they start to feel better.

Patients or their carers should be made aware of the symptoms and signs of liver disorder (e.g. anorexia, nausea, vomiting, abdominal pain, dark urine) and advised to seek immediate medical attention if these develop.
**Amphotericin**

**Drug Class:** Polyene antifungals

**Other commonly used drugs in this class:** Nystatin

**Mode of Action**

**Target:** Ergosterol in fungal cell membrane

**Action:** Binding

**Effect:** The drug molecule has a hydrophilic core which creates a transmembrane ion channel (i.e. a pore) in the fungal cell membrane, increasing its permeability

**Overall effect:** Polyene antifungals cause leakage of intracellular macromolecules and ions including potassium, leading to gross disturbances in ion balance and fungal cell death

**Clinical indications:**

- Systemic fungal infections e.g. histoplasmosis, aspergillosis, cryptococcal meningitis
- Candidiasis of the skin and mucous membranes (nystatin)

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Prescribing and Safety

Amphotericin – first dose 1mg over 20-30 minutes then 250 micrograms daily; given intravenously
Nystatin – given topically, too toxic for systemic administration

Adverse effects

Common:
- GI disturbance e.g. nausea, vomiting, diarrhoea, electrolyte disturbances – hypokalaemia and hypomagnesaemia

Important:
The following apply to amphotericin only:
- Nephrotoxicity
- Neurotoxicity including peripheral neuropathy and encephalopathy
- Cardiotoxicity including arrhythmias and blood pressure changes
- Anaphylaxis

Contra-indications and cautions
- Avoid in pregnancy and renal impairment

Interactions
- NSAIDs (increased risk of haemorrhage)
- ACE inhibitors, ARBs (increased risk of hyperkalaemia)
- Antiplatelet agents (increased risk of haemorrhage)

Therapeutic drug monitoring

Safety: Monitoring tests should include daily FBC, LFT and U+E (including potassium and magnesium concentrations)

Efficacy: Resolution of infection

Additional information:

There is a risk of anaphylaxis with all formulations of intravenous Amphotericin – although rare, it is advised that each patient is given a ‘test dose’ before the first infusion and observed for 30 minutes for anaphylactoid reactions. In patients who have previously experienced acute adverse reactions but still require Amphotericin, prophylactic antipyretics or hydrocortisone can be given.

If concerned about toxicity or renal impairment in your patient with the conventional form of Amphotericin, less toxic lipid formulations are available. Avoid rapid infusion as this increases the risk of cardiac arrhythmias. Nystatin is too toxic for systemic administration.

The different formulations of Amphotericin are not interchangeable and doctors should specify a brand name when prescribing this medication.
**Aciclovir**

**Drug Class:** Antivirals

**Other commonly used drugs in this class:** Famciclovir, Valaciclovir

**Mode of Action**

![Diagram of aciclovir mode of action](image_url)

Aciclovir (and related drugs) are guanosine analogues which are phosphorylated in infected cells by viral thymidine kinase to the active form, aciclovir triphosphate.

**Target:** Viral DNA polymerase

**Action:** Competitive inhibitor

**Effect:** Aciclovir triphosphate competes with the natural nucleotide as a substrate to viral DNA polymerase for incorporation into viral DNA – once incorporated, the drug molecule acts as a nucleotide chain terminator and therefore prevents viral DNA replication

**Overall effect:** Stops viral replication

**Clinical indications:**

Herpes simplex and varicella zoster infections
Prescribing and Safety

Aciclovir: 200mg 5 times daily (4 times daily for immunocompromised prophylaxis or prevention of recurrence) in herpes simplex; 800mg 5 times daily in varicella and herpes zoster

Reduce dose in renal impairment.

Adverse effects

Common:
- GI disturbance e.g. nausea, vomiting, diarrhoea
- Headache

Important:
- Neurotoxicity e.g. dizziness, confusion, hallucinations, convulsions
- Acute renal failure

Contra-indications and cautions
- Caution in the elderly and those with renal impairment

Interactions
- Theophylline (increased plasma theophylline concentration)

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects; monitor renal function regularly in elderly patients who are on IV or long-term therapy

Efficacy: Resolution of infection

Patient communication:

Advise patients to drink plenty of fluids while taking this medication to ensure they maintain adequate hydrations – this is particularly important with patients who are on a high dose, those receiving the drug by infusion or those with renal impairment.

Explain to patients that they should complete the course of their medication as opposed to stopping it when they start to feel better.

Additional information:

Patients can become resistant to aciclovir and related drugs as a result of deficient thymidine kinase activity – in this case the alternative is Foscarnet.

These drugs can also be given topically for skin and eye disease.
Endocrine system

Insulin

**Drug Class:** Insulins

**Commonly used drugs in this class:**
- Rapid acting – insulin lispro (Humalog), insulin aspart (Novorapid)
- Short acting – soluble insulin (Actrapid, Humulin S)
- Intermediate acting – isophane insulin (Insulatard)
- Long acting – insulin glargine (Lantus), insulin determir (Levemir)

**Mode of Action**

Exogenous insulins mimic the action of the body’s own insulin:

**Target:** \( \alpha \)-subunit on insulin receptor

**Action:** Binding – leads to activation of tyrosine kinase domain on \( \beta \) subunit

**Effect:** Various cellular responses including recruitment of glucose transporters to the cell surface in skeletal muscle and adipose tissue. This increases glucose uptake by target tissues, increases glycogen synthesis in the liver, inhibits glycogenolysis and gluconeogenesis in the liver

**Overall effect:** Lowers blood glucose

**Clinical indications:**
- Type 1 diabetes mellitus
- ‘Last resort’ in type 2 diabetes mellitus where lifestyle measures and other drug treatments have failed
- Control of diabetes mellitus (type 1 and 2) during pregnancy
- Component of the emergency management of hyperkalaemia

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety
Dosing regimens vary in complexity and depend on the patient’s ability to comply. Examples include:

- Short acting insulin with each meal and long acting insulin overnight (Basal bolus regimen)
- Mixture of short and intermediate acting insulins given twice daily

Adverse effects:
Common:
- Weight gain
- Local allergic reaction e.g. erythema, pruritus

Important:
- Hypoglycaemia
- Lipodystrophy, lipo hypertrophy

Contra-indications and cautions

Interactions
- Beta blockers (enhanced hypoglycaemic effect AND hypo warning signs e.g. tremor possibly masked)
- Other hypoglycaemic agents e.g. sulphonylureas
- Corticosteroids (reduced hypoglycaemic effect)

Therapeutic drug monitoring
Safety/Efficacy: Patients will normally monitor their own blood sugars throughout the day by pricking their finger and checking capillary glucose. If DKA is suspected, check ketones.

Patient communication:
Explain to patients where they should inject their insulin – main sites are stomach, thighs and buttocks. Patients MUST NOT inject their insulin into a vein. Also explain the importance of varying where they inject their insulin regularly, both within the same site and between sites. This is because repeatedly using a single site leads to fat changes which can alter the absorption of insulin.

Advise patients that they should aim to maintain a blood glucose between 4 and 7mmol/l before meals and less that 9mmol/l after meals.

Go over the insulin ‘sick day rules’ with the patient – when unwell:
- Never stop taking your insulin or omit doses – your sugars can still rise even when you aren’t eating
- Measure your blood sugars more often – if greater than 10mmol/l, consider taking a larger or additional dose of rapid acting insulin
- If blood glucose levels are >13mmol/l or you are vomiting, check your urine or blood for ketones
- Drink lots of fluids (aim for 3 litres a day) as it is easy to become dehydrated when you are unwell, particularly if there is vomiting/diarrhoea/fever
- Try to stick to your normal diet as much as possible, if you cannot manage solids take liquids
- If unable to keep fluids down, go to A&E

Explain the importance of avoiding hypoglycaemic episodes when the blood glucose falls below 4 mmol/l. Patients will normally have ‘warning signs’ that their sugars are low. However, with repeated hypos these signs are blunted and patients may lose their awareness of this. During such periods it is important that patients DO NOT drive or operate machinery.

Ensure patients know what to do if they have a ‘hypo’ as these can occur in patients taking insulin for many reasons e.g. dose too high, eating smaller meals than normal, exercising more, losing weight. If this happens repeatedly the patient should notify their doctor who may change their dose.

Drivers treated with insulin should normally check their sugars before driving. On long journeys they should also check sugars every 2 hours. Advise patients to keep a supply of sugar in their vehicle at all times. If sugars do start to go low while driving, patients should:
- Stop the vehicle in a safe place
- Switch off the ignition
- Eat or drink a suitable source of sugar
- Wait until recovery is complete and blood sugars have normalised before resuming the drive

As there is a large variety in the types of injecting devices, you should check dispensed items with patients to ensure that he/she has been given what he/she is expecting.

Additional information:
- When prescribing insulin for hospitalised patients on a drug kardex, **DO NOT ABBREVIATE THE WORD ‘UNITS’** as u or iu – write out in full
- Rapid/short acting insulins start to work in minutes and bring down the blood glucose within 2-4 hours – these are used for food or to bring down a high blood glucose
- Intermediate/long acting insulins are used for background action or to work later in the day
- If giving insulin intravenously, the infusion must be diluted e.g. 50 units actrapid insulin in 50ml 0.9% sodium chloride
- Insulin cannot be given orally as it is degraded in the GI tract
**Gliclazide**

**Drug Class:** Sulfonylureas

**Other commonly used drugs in this class:** Glibenclamide, Glipizide, Tolbutamide

**Mode of Action**

Target: High-affinity sulfonylurea receptors on the ATP-sensitive K⁺ channels on β islet cell plasma membranes

Action: Block K⁺ channels

Effect: Reduced K⁺ efflux leading to β cell depolarisation, Ca²⁺ entry and insulin secretion

Overall effect: Increased insulin levels leading to increased glucose uptake by target tissues and reduction in plasma glucose

**Clinical indications:**

First line in type 2 diabetics with BMI<25, adjunct in type 2 diabetics with BMI>25 who are not adequately controlled on metformin.

NB. Sulfonylureas require functional beta cells in order to work – they are most useful in the earlier stages of type 2 diabetes.
Prescribing and Safety

Gliclazide:
Starting dose – 40-80mg daily with food
Maintenance dose – up to 320mg daily in divided doses

Adverse effects:
Common:
- GI disturbance (nausea, vomiting, diarrhoea, constipation)
- Weight gain

Important:
- Hypoglycaemia
- Hyponatraemia
- Hepatotoxicity – cholestatic jaundice, hepatitis, hepatic failure
- Hypersensitivity – allergic skin reactions, may progress to erythema multiforme/exfoliative dermatitis

Contra-indications and cautions
- Caution in renal impairment (avoid if severe), the elderly and in overweight/obese patients due to possible weight gain
- Avoid/hold in the presence of ketoacidosis, avoid in hepatic impairment, pregnancy and breastfeeding

Interactions
- Warfarin (increased hypoglycaemic effect)
- Antifungals (increased hypoglycaemic effect) – fluconazole, miconazole
- Alcohol (increased hypoglycaemic effect)
- Beta blockers (hypoglycaemia warning signs e.g. tremor may be masked)
- MAOIs (increased hypoglycaemic effect)

Therapeutic drug monitoring
Efficacy: Blood glucose and HbA1c should be checked to determine the patient’s level of glycaemic control

Patient communication:
Reinforce with patients the warning signs of hypoglycaemia and advise them to take some form of sugar (lucozade, fruit juice, etc.) if these arise. If patients are experiencing regular ‘hypos’ they should inform their doctor as the dose of their medication may need to be reduced.
Metformin

Drug Class: Biguanides

Other commonly used drugs in this class: None

Mode of Action

Target: AMP-kinase, an enzyme involved in regulating cellular energy metabolism

Action: The exact mechanism is unclear but metformin acts to increase the sensitivity of peripheral tissues to insulin and inhibits gluconeogenesis in the liver

Effect: Increases glucose uptake and utilisation in target tissues (skeletal muscle); reduces hepatic glucose output

Overall effect: Lowers blood glucose level

Clinical indications:

- First line therapy in overweight patients (BMI>25) with type II diabetes mellitus (who have failed on diet/exercise measures)
- Adjuvant therapy in normal weight patients (BMI<25) who do not achieve adequate glycaemic control on sulphonylureas
Prescribing and Safety

500mg 2-3 times daily

Adverse effects

Common:
- GI disturbances e.g. anorexia, nausea, vomiting, diarrhoea
- Taste disturbance (metallic taste)

Important:
- Lactic acidosis

Contra-indications and cautions
- Caution in renal impairment due to increased risk of lactic acidosis (avoid if severe)
- Avoid in ketoacidosis
- Hold metformin for at least 48 hours in patients undergoing iodine contrast imaging due to risk of acute renal failure

Interactions
- ACE inhibitors (increased hypoglycaemic effect)
- MAOIs (increased hypoglycaemic effect)

Therapeutic drug monitoring

Safety: U+E and eGFR should be performed before starting metformin to determine baseline renal function – this should be re-checked at least once a year (twice a year in those with renal impairment)

Efficacy: Reduction in serum glucose and HbA1c, improved glycaemic control

Patient communication

Explain to patients that this medication should be taken with food (a small amount is sufficient).

Additional comments

The GI side effects of Metformin can be minimised by lowering the dose or using a modified-release preparation. Metformin does NOT affect the secretion of insulin – it only increases the body’s response to the insulin which is already present. It therefore does not induce hypoglycaemia.

Metformin requires the presence of endogenous insulin in order to function – if the patient has no functioning pancreatic beta cells this drug will be ineffective.
**Liraglutide**

**Drug Class:** GLP-1 analogues

**Other commonly used drugs in this class:** Exenatide

**Mode of Action**

**Target:** Glucagon-like peptide-1 (GLP-1) receptors

**Action:** GLP-1 analogues bind to and activate the receptors in the same way as the endogenous hormone

**Effect:** Increase synthesis and release of insulin by pancreatic β cells, suppress inappropriate glucagon secretion from pancreatic α cells

**Overall effect:** Increase glucose uptake by target tissues, inhibit glucagon secretion, reduce hepatic glucose output, delay gastric emptying and promote satiety → reduced blood glucose levels

**Clinical indications:**

Can be used as second or third line therapy for type 2 diabetes mellitus in specific circumstances (see NICE guideline on management of type 2 diabetes)
Prescribing and Safety

GLP-1 analogues are given by subcutaneous injection.

Liraglutide: Starting dose – 0.6mg once daily
  Maintenance dose – 1.2-1.8mg once daily
Exenatide: 5 micrograms twice daily

Adverse effects

Common:
  • GI disturbance

Important:
  • Severe pancreatitis including haemorrhagic/necrotising pancreatitis – potentially fatal
  • Hypoglycaemia
  • Antibody formation against exenatide (may reduce efficacy)

Contra-indications and cautions

  • Caution in the elderly and those with renal impairment
  • Avoid in ketoacidosis, diabetic gastroparesis and severe GI disease including inflammatory bowel disease
  • Discontinue immediately and permanently if patient develops acute pancreatitis

Interactions

  • Warfarin (increased anticoagulant effect)
  • Other antidiabetic drugs (enhanced hypoglycaemic effect – may need to alter dosages accordingly)

Therapeutic drug monitoring

Safety: Monitor clinically for adverse effects

Efficacy: Reduction in blood glucose and HbA1c levels, improved glycaemic control

Patient communication:

Patients or their carers should be made aware of the symptoms and signs of acute pancreatitis e.g. severe persistent abdominal pain, nausea, vomiting and advised to seek immediate medical attention if these develop.

Explain to patients that if they miss a dose of their medication, they should continue with the next dose AS SCHEDULED – they should not take a dose after a meal.

Additional information: The action of GLP-1 analogues is glucose dependent – as plasma glucose levels fall, insulin secretion also falls.
**Pioglitazone**

**Drug Class:** Thiazolidinediones

**Other commonly used drugs in this class:** None

**Mode of Action**

**Target:** PPARγ receptors in adipose tissue, skeletal muscle and liver (insulin target tissues) – these are complexed with retinoid X receptor (RXR)

**Action:** Agonist

**Effect:** Causes the PPARγ-RXR complex to bind to DNA, promoting transcription of a number of genes whose products are involved in insulin signalling e.g. lipoprotein lipase, Glut-4. This increases the sensitivity of tissues to insulin by recruiting glucose transporters to cell surface.

**Overall effect:** Thiazolidinediones reduce insulin resistance leading to enhanced uptake of glucose/fatty acids and a reduction in blood glucose levels.

NB. Thiazolidinediones are only effective in the presence of insulin (either endogenous or injected)

**Clinical indications:**

- Third line treatment option for type 2 diabetes mellitus when control is inadequate with metformin and a sulphonylurea
- Second line treatment option for type 2 diabetes mellitus if a sulphonylurea is contraindicated or there is significant risk of hypoglycaemia

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Starting dose – 15-30mg once daily

Maintenance dose – up to 45mg once daily according to response

Adverse effects

Common:
- Anaemia; arthralgia; dizziness; gastro-intestinal disturbances; haematuria; headache; hypoesthesia; impotence; oedema; vertigo; visual disturbances; weight gain

Important:
- Liver dysfunction

Contra-indications and cautions

- Caution in cardiovascular disease
- Avoid in patients with hepatic impairment, those with a history of heart failure and those at increased risk of fracture
- Discontinue if patient develops jaundice

Interactions

- Insulin – risk of heart failure, use this combination with caution/avoid
- Beta blockers (may mask warning signs of hypoglycaemia e.g. tremor)
- Other antidiabetic drugs (enhanced hypoglycaemic effect – may need to alter dosages accordingly)

Therapeutic drug monitoring

Safety: Check LFT at baseline and monitor periodically every 2-6 months thereafter

Efficacy: Reduction in blood glucose and HbA1c levels, improved glycaemic control

Patient communication:

Make patients or their carers aware of the symptoms and signs of liver impairment e.g. nausea, vomiting, abdominal pain, dark urine and advise them to seek immediate medical attention if any of these develop.

Additional information:

In surgical patients, convert to insulin during the perioperative period. Hold pioglitazone on the morning of surgery and restart when the patient is eating and drinking normally again.

Thiazolidinediones increase the risk of bone fractures, particularly in women.

If combining pioglitazone with a sulphonylurea or insulin, the dose of these drugs may need to be reduced.

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**Sitagliptin**

**Drug Class:** DPP4 inhibitors

**Other commonly used drugs in this class:** Saxagliptin, Vildagliptin

**Mode of Action**

![Diagram of Sitagliptin action](image)

**Target:** Dipeptidyl peptidase 4 (DPP4) enzymes

**Action:** Competitive inhibitor

**Effect:** Inhibit degradation of incretin hormones GLP-1 and GIP by DPP4 enzymes. This increases levels of GLP-1 and GIP leading to increased synthesis and release of insulin by pancreatic β cells. Glucagon secretion from pancreatic α cells is also reduced.

**Overall effect:** Increase glucose uptake by target tissues, inhibit glucagon secretion, reduce hepatic glucose output, delay gastric emptying and promote satiety → reduced blood glucose levels

**Clinical indications:**

- Third line treatment option for type 2 diabetes mellitus when control is inadequate with metformin and a sulphonylurea
- Second line treatment option for type 2 diabetes mellitus if a sulphonylurea is contraindicated or there is significant risk of hypoglycaemia
Prescribing and Safety

Sitagliptin – 100mg once daily

Saxagliptin – 5mg once daily

Vildagliptin – 50-100mg daily

Adverse effects

Common:
- Upper respiratory tract infection/nasopharyngitis
- GI disturbance

Important:
- Hypoglycaemia
- Pancreatitis
- Hepatotoxicity (vildagliptin only)

Contra-indications and cautions
- Caution in the elderly and those with heart failure, hepatic or renal impairment (avoid if severe)
- Avoid in ketoacidosis

Interactions
- Digoxin (increased plasma concentration with sitagliptin)
- Other antidiabetic drugs (enhanced hypoglycaemic effect, may need to alter dosages accordingly)

Therapeutic drug monitoring

Safety: Patients started on vildagliptin should have baseline LFT at start of treatment – this should be re-checked every 3 months

Efficacy: Reduction in blood glucose and HbA1c levels, improved glycaemic control

Patient communication:

Make patients on Vildagliptin (or their carers) aware of the symptoms and signs of liver impairment e.g. nausea, vomiting, abdominal pain, dark urine and advise them to seek immediate medical attention if any of these develop.

Additional information:

NICE recommends that DPP4 inhibitor therapy should only be continued if HbA1c is reduced by at least 0.5% (5.5mmol/mol) within 6 months of starting treatment.
Levothyroxine

Drug Class: Thyroid hormones

Other commonly used drugs in this class:

Mode of Action

Target: Thyroid nuclear receptor (receptor superfamily 4)

Action: Agonist

Effect: stimulates nuclear transcription of target genes, increasing mRNA and protein synthesis

Overall effect: restore euthyroid state through synthetic replacement of deficient endogenous thyroid hormone

Clinical indications:

- Hypothyroidism
- ‘Replace’ component of block and replace regimen for hyperthyroidism
- Diffuse non-toxic goitre, Hashimoto’s thyroiditis, thyroid carcinoma

Prescribing and Safety

Starting dose: 50-100 micrograms daily (before breakfast)
Dose increased in steps of 25-50 micrograms every 3-4 weeks according to response
Maintenance dose: 100-200 micrograms daily (50-200 micrograms daily in cardiac disease, severe hypothyroidism, patients over 50 years)

Adverse effects:
Usually at excessive dosage, mimic symptoms and signs of hyperthyroidism:

Diarrhoea, vomiting, anginal pain, arrhythmias, palpitations, tachycardia, tremor, restlessness, excitability, insomnia, sweating, heat intolerance, weight loss

Contra-indications and cautions

- Caution in elderly patients, those with cardiovascular disease, long standing hypothyroidism, diabetes insipidus, diabetes mellitus (dose of antidiabetic drugs may need to be increased), panhypopituitarism and predisposition to adrenal insufficiency
- Avoid in patients with thyrotoxicosis

Interactions

- Warfarin (enhanced anticoagulant effect)
**Therapeutic drug monitoring**

**Safety:** Clinical signs and symptoms of excessive dosage (see adverse effects) should prompt prescriber to reduce the dose of levothyroxine accordingly; in pregnancy, monitor serum thyrotrphin concentration

**Efficacy:** Clinical review to determine if symptoms are improving/have resolved, thyroid function tests to check T3/T4 and TSH levels are within normal range

Patients who have TFTs within normal range (with or without thyroxine) but remain symptomatic should be investigated further for a non-thyroid cause of symptoms.

**Patient communication:**
Explain to patients that this is a lifelong treatment for hypothyroidism and they should not stop taking their medication.
Carbimazole

**Drug Class:** Antithyroid drugs/Thioureylenes

**Other commonly used drugs in this class:** Propylthiouracil

**Mode of Action:** precise mechanism of action unclear, it is thought to involve:

![Diagram of Carbimazole (Pro-drug) and Thyroid Peroxidase]

- **Target:** Thyroid peroxidase enzyme
- **Action:** Inhibitor
- **Effect:** Inhibits the iodination of tyrosyl residues in thyroglobulin, inhibits coupling of iodothyronine molecules
- **Overall effect:** Reduces output of thyroid hormones T3 and T4 from the thyroid gland, leading to a gradual reduction in hyperthyroid signs and symptoms

**Clinical indications:**

Hyperthyroidism – either alone as part of a block regimen to restore euthyroid status or in combination with levothyroxine as the block component of a ‘block and replace’ regimen

**Prescribing and Safety**

**Block:**
- Starting dose – 15-40mg once daily
- Maintenance dose – 5-15mg once daily for 18 months

**Block and replace:**

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Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
40-60mg once daily plus 50-150 micrograms Levothyroxine once daily for 18 months

**Adverse effects:**
**Common:**
- GI disturbance, arthritis, fever, rash, pruritus, jaundice

**Important:**
- Agranulocytosis, neutropenia (carbimazole)

**Contra-indications and cautions**
- Caution in hepatic impairment (avoid if severe) and during pregnancy
- Avoid in patients with severe blood disorders
- Discontinue carbimazole if patient develops clinical or laboratory evidence of neutropenia

**Therapeutic drug monitoring**

**Safety:** Monitor patients for signs and symptoms of bone marrow suppression, check FBC if there is clinical evidence of infection

**Efficacy:** Clinically – Reduction in signs and symptoms of hyperthyroidism, restoration of euthyroid status

Thyroid function tests – T4 reduced to within normal limits, TSH increased to within normal limits

**Patient communication:**
**Advised patients to report any symptoms and signs suggestive of infection, especially sore throat.**

Explain to female patients taking antithyroid drugs as part of the block and replace regimen that they should inform their doctor immediately if they become pregnant so that their medication can be adjusted accordingly.

**Additional information:**

THE BLOCK AND REPLACE REGIMEN IS NOT SUITABLE DURING PREGNANCY. In addition, propylthiouracil is preferred to carbimazole during pregnancy.
**Prednisolone**

**Drug Class:** Corticosteroids

**Other commonly used drugs in this class:** Dexamethasone, Hydrocortisone, Methylprednisolone

**Mode of Action**

**Target:** Intracellular steroid receptors

**Action:** Agonist – prednisolone and other corticosteroids mimic the action of the endogenous mediator cortisol at steroid receptors

**Effect:** Binding of a corticosteroid to the cytoplasmic steroid receptor exposes a DNA binding domain on the receptor. This allows the steroid-receptor complex to associate with glucocorticoid response elements present in the promoter regions of target genes.

**Overall effect:** Upregulation of gene transcription

**Clinical indications:**

- Suppression of inflammatory and allergic disorders
- Inflammatory bowel disease
- Severe asthma (step 5)
- Immunosuppression
- Rheumatic disease

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Prescribing and Safety

Prednisolone:
Starting dose – 15-60mg mane after breakfast depending on indication
Maintenance dose – 2.5-15mg daily

Adverse effects:

- Moon face with plethoric cheeks
- Steroid induced cataracts
- Steroid induced psychosis
- Buffalo hump fat distribution
- Central fat distribution with striae
- Thin limbs with paper money skin and easy bruising
- Hypertension
- Steroid induced diabetes mellitus
Contra-indications and cautions
- Caution in pregnancy (risk of intrauterine growth restriction)

Interactions
- Antihypertensives (reduced hypotensive effect)
- NSAIDs (increased risk of peptic ulceration and bleeding)
- Antidiabetics (reduce hypoglycaemic effect)
- Wafarin (may enhance or reduce anticoagulant effect)
- Live vaccines – avoid concomitant use due to increased risk of infection

Therapeutic drug monitoring
Safety: Patient should be monitored clinically to detect adverse effects

Efficacy: Depends on indication – improvement in symptoms, reduced frequency of asthma attacks, etc.

Patient communication:
Every patient started on systemic corticosteroid therapy should be given a written patient information leaflet.
Inform patients that this medication suppresses their immune system and therefore puts them at increased risk of infection. In particular they are considered at high risk of severe chickenpox and should avoid close contact with people who have chickenpox or shingles. The same applies to measles.
Due to the adrenal suppression caused by corticosteroids which can last for a year or more after stopping treatment, explain to patients that they must mention the course of steroids when receiving treatment for any illness or injury.
Patients should be warned that this medication can cause changes in their mood and behaviour – if they are worried about any such psychological changes they should seek medical advice.
Patients should also be issued with a steroid treatment card which they should carry with them at all times.

Additional comments:
Do not stop corticosteroids suddenly as this can lead to acute adrenal insufficiency, hypotension or death. Steroids must be withdrawn gradually by reducing down the dose over a period of time (determined on a case-by-case basis).

Prescribers should consider the concomitant prescribing of bisphosphonates if prednisolone treatment is long term.
Alendronic acid (Alendronate)

Drug Class: Bisphosphonates

Other commonly used drugs in this class: Clodronate, Pamidronate, Risedronate

Mode of Action

**Action/Effect:** Bisphosphonates adsorb onto hydroxyapatite crystals on the surface of bone. When osteoclasts start to resorb this bone the bisphosphonate is released. This interferes with formation of the osteoclast ruffled border and impairs the osteoclast’s ability to adhere to bone and produce the protons needed for continued resorption. Bisphosphonates also promote osteoclast apoptosis while inhibiting the apoptosis of bone-forming osteoblast cells.

**Overall effect:** Prevents further reduction in bone mass

**Clinical indications:**

- **Prophylaxis and treatment of osteoporosis including corticosteroid-induced osteoporosis**
- Hypercalcaemia of malignancy
- Paget’s disease of bone
- Osteolytic lesions and bony metastases
Prescribing and Safety

Alendronic acid – 10mg daily

Adverse effects

Common:
- GI disturbance; alopecia; asthenia; dizziness; headache; joint swelling; musculoskeletal pain; oesophageal reactions; peripheral oedema; pruritus

Important:
- Osteonecrosis of the jaw
- Oesophagitis may be severe with stricture formation
- Atypical stress fractures with long term use

Contra-indications and cautions

- Caution in renal impairment (avoid if severe)
- Avoid in pregnancy, hypocalcaemia and in patients with oesophageal abnormalities e.g. strictures, achalasia

Interactions

- Antacids (reduced bisphosphonate absorption)
- Aminoglycoside antibiotics (increased risk of hypocalcaemia)
- Oral iron (reduced bisphosphonate absorption)

Therapeutic drug monitoring

Safety: Consider dental check-up before starting a bisphosphonate due to the risk of osteonecrosis of the jaw, particularly if the patients is receiving intravenous bisphosphonates or is considered to have poor dental hygiene.

Efficacy: Bone mineral density scan (Dexa scan) as required

Patient communication:

Explain to patients that this medication should be taken on an empty stomach 30 minutes before breakfast. The tablet should be swallowed whole with plenty of water while sitting or standing and the patient should remain sitting or standing for 30 minutes after taking the tablet.

Patients should also be advised to stop taking this medication and seek medical attention if they notice any symptoms of oesophageal dysfunction e.g. difficulty swallowing, new or worsening heartburn.

To minimise the risk of osteonecrosis of the jaw, advise patients to maintain good oral hygiene, have regular routine dental check-ups and report any oral symptoms arising during treatment.
Obstetrics, gynaecology and urinary-tract disorders

Oral Contraceptives

Mode of Action

**Combined Oral Contraceptive Pill (COCP)** – The COCP contains both oestrogen and progestogen and has a dual mode of action:

- Oestrogen and progesterone inhibit the release of gonadotrophin-releasing hormone from the hypothalamus by negative feedback. This in turn reduces the levels of follicle stimulating hormone (FSH) and luteinising hormone (LH). The absence of FSH prevents follicular development, which lack of an LH surge inhibits ovulation.

- Progesterone reduces the water content of cervical mucus and increases its viscosity – this inhibits the passage of sperm through the cervix and into the upper genital tract (uterus, fallopian tubes)

**Progestogen Only Pill (POP)** – this pill contains only progestogen with no oestrogen. It alters the endometrium and cervical mucus as above, but only inhibits ovulation in around 40% of women.

Clinical indications:

- Contraception
- Menstrual symptoms (COCP only)
- Treatment of acne vulgaris in women

Prescribing and Safety

One pill daily for 21 days followed by 7 pill free days in each month

Adverse effects:

Common:
- Menstrual irregularity

Important:
- **Venous thromboembolism** – the OCP is a risk factor for DVT/PE
- **MI/stroke** – the COCP is a risk factor for these events, particularly those with higher oestrogen content
- Hypertension
- Hepatic tumours

Contra-indications and cautions

- Caution in diabetes mellitus, inflammatory bowel disease, migraine sufferers and those with other risk factors for thromboembolic and cardiovascular disease e.g. smoking, obesity
- Avoid in patients with a history of thromboembolic disease, those with existing cardiovascular disease, hyperlipidaemia, gallstones, cholestatic jaundice and in patients with history of breast cancer
- Discontinue if patient develops symptoms or signs of DVT, PE, MI, stroke or liver disease
- Oestrogen-containing pills should be stopped 4 weeks before any major or lower limb surgery

**Interactions**
- Antihypertensives (reduced hypotensive effect)
- Antiepileptics (reduced contraceptive effect)
- St. John’s Wort (reduced contraceptive effect)

**Therapeutic drug monitoring**

**Safety:** Patients on the COCP should have their blood pressure checked at the start of treatment and monitored periodically for the first year e.g. every 3 months when getting repeat prescription

**Efficacy:** Depends on indication – prevention of pregnancy, improvement/resolution of acne

**Patient communication:**

Advise patients that this medication should be taken at approximately the same time each day – if a pill is missed the contraceptive protection may be diminished. It is best to start taking the pill on the first day of a menstrual period as this affords contraceptive protection straight away.

Explain to patients that they may experience a small amount of bleeding between periods, particularly in the first few months after starting this medication. This is usually normal, however women should be advised to see their doctor if this continues for more than a few months or does not go away after they have stopped taking the pill.

Patients should be made aware of the symptoms and signs of DVT, PE, MI etc. and advised to seek immediate medical attention if any of these develop.

Women should be reminded of the importance of attending for regular cervical smear tests when called, particularly as this medication can increase the risk of cervical cancer.

Explain to patients that severe vomiting or diarrhoea can reduce absorption of the pill – if they become ill in this way for >24 hours it is advisable to use additional contraceptive measures for 7 days.

Compliance is of utmost importance. If compliance is likely to be an issue, the patient and prescriber could consider a variety of formulations other than an oral tablet that might suit the patient’s needs e.g. patch, or depot injection.

**Additional comments:**

The COCP has a protective effect against endometrial and ovarian malignancy but is associated with a slight increase in the risk of breast and cervical cancer.
Malignant disease and immunosuppression

Methotrexate

Drug Class: Disease modifying anti-rheumatic drugs (DMARDs)

Other commonly used drugs in this class:

Mode of Action

Target: Dihydrofolate reductase enzyme

Action: Competitive inhibitor

Effect: Inhibits reduction of dihydrofolate to its active form tetrahydrofolate

Overall effect: Immunosuppressant activity

Clinical indications:

- Rheumatoid arthritis
- Malignant disease – used as an anti-metabolite in cancer therapy
- Crohn’s disease
Prescribing and Safety

Rheumatology: dose range 5-25mg once weekly
Gastroenterology: Starting dose – 25mg once weekly for 16 weeks
   Maintenance dose – 15mg once weekly

Always prescribe methotrexate in multiples of the 2.5mg tablet strength

Adverse effects:
Common:
- Nausea, diarrhoea
- Alopecia
- Stomatitis – stop treatment if this occurs, mucositis

Important:
- Myelosuppression including leucopenia and neutropenia
- Hepatotoxicity
- Pulmonary fibrosis, interstitial pneumonitis
- Pericarditis, pericardial tamponade

Contra-indications and cautions
- Caution in ulcerative colitis, peptic ulcer disease and ulcerative stomatitis
- Avoid in pregnancy and breastfeeding, severe hepatic or renal impairment, blood disorders (severe anaemia, leucopenia or thrombocytopenia), untreated folate deficiency and history of alcohol abuse/cirrhosis
- Hold methotrexate temporarily if patient is systemically unwell with significant infection requiring anti-infective intervention

Interactions
- Trimethoprim/co-trimoxazole (risk of pancytopenia, do not co-prescribe)
- NSAIDs (may reduce methotrexate excretion but unlikely to cause clinically significant adverse effects, concomitant use common in rheumatic disease)
- Clozapine (increased risk of agranulocytosis – avoid concomitant use)
- Acitretin (increased plasma methotrexate concentration, increased risk of hepatotoxicity – avoid concomitant use)
- Live vaccines (high risk of infection due to immunosuppressive effect of methotrexate)

Therapeutic drug monitoring
Safety: Baseline tests should include FBC, U&E, LFT, ESR and CRP. Selected patients may require pulmonary function testing and CXR. FBC, U&E and LFT should be checked every 1-2 weeks until patient is stabilised and then every 2-3 months thereafter (monthly in rheumatology). ESR and CRP should be re-checked every 3 months.

Also ask about oral ulceration/sore throat, unexplained rash or unusual bruising at every consultation.

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
**Efficacy:** Depends on indication e.g. improvement in symptoms of rheumatoid arthritis, reduced frequency of flares

**Patient communication:**
Explain to female patients that they must not take this medication during pregnancy. Both men and women should be advised to use reliable contraception throughout treatment and for 3 months after stopping methotrexate. If a patient or their partner does become pregnant while on methotrexate they should inform their doctor immediately and the medication should be stopped.

Patients should be advised to avoid taking NSAIDs unless prescribed by their doctor.

Advise patients that they should immediately report to their doctor any features of blood disorder (sore throat, bruising, mouth ulcers), liver toxicity (nausea, vomiting, abdominal discomfort, dark urine) or respiratory effects e.g. shortness of breath.

**Additional comments:**
When starting a patient on methotrexate you should also prescribe folic acid at a dose of 5mg to be taken once weekly, 1-2 days after the methotrexate dose.

Patients with significant pleural effusion should have this drained prior to starting methotrexate because the drug may accumulate in this fluid and cause myelosuppression on returning to the circulation.
Azathioprine

Drug Class: DMARD/antimetabolite

Other commonly used drugs in this class:

Mode of Action

Target: Azathioprine is metabolised to the 6-mercaptopurine, which is then converted intracellularly to purine analogues. These purine analogues are incorporated into DNA and inhibit clonal expansion of B lymphocytes during the induction phase of the immune response. This results in suppression of the antibody-mediated response.

Clinical indications:

- Rheumatoid arthritis
- Rejection prophylaxis in organ transplantation
- Autoimmune disease
  - Systemic lupus erythematosus (SLE)
  - Idiopathic thrombocytopenic purpura (ITP)
  - Pemphigus vulgaris
  - Autoimmune hepatitis
- Inflammatory bowel disease

Prescribing and Safety

1-3mg/kg daily depending on the patient and the condition, reduce in hepatic or renal impairment
Adverse effects:

Common:
- Nausea

Important:
- Cancer risk – azathioprine increases the risk of lymphoma and skin malignancies
- Bone marrow suppression – anaemia, leucopenia, thrombocytopenia
- Hypersensitivity reactions including interstitial nephritis – discontinue immediately
- Pancreatitis

Contra-indications and cautions
- Caution in patients with known hypersensitivity to mercaptopurine, those with thiopurine methyltransferase (TPMT) deficiency and in breastfeeding women

Interactions
- **Allopurinol** (risk of severe myelosuppression – do not co-prescribe)
- Warfarin (reduced anticoagulant effect) – may need to increase warfarin dose
- Aminosalicylates (bone marrow toxicity – may require increased monitoring
- Trimethoprim/co-trimoxazole (risk of blood disorders)

Therapeutic drug monitoring

**Safety**: Baseline tests should include FBC, LFT, U&E, ESR and CRP (may also wish to measure Thiopurine methyltransferase (TPMT)) level prior to starting – at discretion of initiating specialist. FBC and LFT should be re-checked weekly for the first 8 weeks or until stable, then monthly thereafter. ESR and CRP should be re-checked every 3 months.

Also ask about oral ulceration/sore throat, unexplained rash or unusual bruising at every consultation.

**Efficacy**: Depends on indication e.g. improvement in symptoms of rheumatoid arthritis, reduced frequency of flares

**Patient communication**:

Explain to patients that this medication increases their risk of skin cancer and it is important that they take appropriate precautions – avoid excessive sun exposure, use high factor sunscreen.

Explain to female patients that if they become pregnant or are planning to become pregnant they should continue to take their medication as normal but should notify their doctor as soon as possible. Both men and women should be advised to use reliable contraception throughout treatment.

Advise patients that they should take this medication with or after food.
**Musculoskeletal and joint diseases**

**Ibuprofen**

**Drug Class:** Non-steroidal anti-inflammatory drugs (NSAIDs)

**Other commonly used drugs in this class:** Diclofenac, Indometacin, Naproxen, Piroxicam

**Mode of Action**

![Diagram of COX-1 and COX-2 enzymes with NSAIDs inhibiting COX-2]

**Target:** Cyclooxygenase-2 (COX-2) enzymes. NB. COX-1 isoform also affected – this is responsible for the main side effects of NSAIDs

**Action:** Inhibitor

**Effect:** Inhibit COX-mediated conversion of arachidonic acid to prostaglandins and thromboxanes which cause vasodilatation, oedema and pain

**Overall effect:** Reduced hyperalgesic and vasodilatory effects in acute inflammation

**NB.** COX-2 selective non-competitive inhibitors e.g. celecoxib, etoricoxib are also available. As these drugs do not inhibit COX-1 the risk of serious upper GI side effects is much less than with traditional NSAIDs. However, the coxibs are associated with an increased risk of thrombotic events such as MI and stroke and should not be used routinely as an alternative to traditional NSAIDs except where specifically indicated e.g. in patients at high risk of GI ulceration or haemorrhage. Any patient being started on coxibs should have a cardiovascular risk assessment as these drugs are contraindicated in those with existing cardiovascular disease.

**Clinical indications:**
- Inflammatory arthritis e.g. rheumatoid arthritis
- Osteoarthritis
- Acute gout
- Mild to moderate pain including dysmenorrhea, dental and orofacial pain
Prescribing and Safety
Ibuprofen: 300-400mg 3-4 times daily, maximum 2.4g daily
Naproxen: 0.5-1g daily

Adverse effects
Common:
• Headache
• Dizziness
Important:
• Gastric irritation, ulceration and bleeding
• Compromised renal blood flow, renal impairment, peripheral oedema
• Increased cardiovascular risk (including increased risk of MI, particularly with COX-1 selective agents)
• Bronchospasm

Contra-indications and cautions
• Caution in asthma, the elderly, patients with allergic disorders, coagulation defects, cardiovascular disease, pregnancy, breastfeeding, hepatic and renal impairment (avoid if severe)
• Avoid in patients with previous or active peptic ulceration (may not be possible in serious rheumatic disease), those with history of hypersensitivity to aspirin or other NSAID and in severe heart failure
• Discontinue if acute renal failure develops

Interactions
• Warfarin (enhanced anticoagulant effect)
• Lithium (reduced excretion, increased risk of lithium toxicity)
• Other nephrotoxic drugs e.g. aminoglycoside antibiotics, ACE inhibitors, ARBs (increased risk of nephrotoxicity)
• Two or more NSAIDs in combination (increased risk of bleeding, especially if one is aspirin)
• Anticoagulants (increased risk of bleeding)
• Antidepressants e.g. SSRIs, venlafaxine (increased risk of bleeding)

Therapeutic drug monitoring
Safety: In renal impairment, monitor renal function via U+E
Efficacy: Depends on indication e.g. improvement in pain or joint stiffness

Patient communication
Advise patients that this medication should be taken with food (a small amount is sufficient).
Contact pharmacist/doctor if GI symptoms arise.
Not for long term use in osteoarthritis.

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Colchicine

**Drug Class:** (Drugs used in gout)

**Other commonly used drugs in this class:** None

**Mode of Action**

**Target:** Tubulin

**Action:** Binds to form a colchicine-tubulin complex

**Effect:** Inhibits polymerisation of neutrophil microtubules by preventing addition of dimers, leading to impaired cell motility and decreases phagocytosis

**Overall effect:** Prevents migration of neutrophils into the joint space, dampening the inflammatory response

**Clinical indications:**

- Acute gout
- Short term cover during initiation of allopurinol therapy
Prescribing and Safety

500 micrograms 2-4 times daily until symptoms relieved

Adverse effects:
Common:
- GI disturbance e.g. nausea, vomiting, abdominal pain, diarrhoea (may be profuse)

Important:
- GI haemorrhage at high doses
- Renal and hepatic damage
- Myopathy, peripheral neuropathy
- Bone marrow suppression

Contra-indications and cautions
- Caution in the elderly, hepatic impairment, renal impairment (avoid if severe) and those with GI or cardiac disease
- Avoid in pregnancy

Therapeutic drug monitoring
Safety: Monitor clinically for adverse effects
Efficacy: Resolution of symptoms

Additional information:
Acute attacks of gout are usually treated with high doses of NSAIDs such as Diclofenac and naproxen (NOT aspirin) – colchicine is a useful alternative in patients in whom NSAIDs are contraindicated.

** Check if patient who presents with gout is on a prescribed thiazide diuretic
Allopurinol

Drug Class:

Other commonly used drugs in this class:

Mode of Action

**Target:** Xanthine oxidase enzyme

**Action:** Competitive inhibitor

**Effect:** Inhibits oxidation of xanthine to uric acid

**Overall effect:** Reduced concentration of insoluble uric acid and urate in tissues

**Clinical indications:**

- Prophylaxis of gout (NOT appropriate in treatment of acute attack)
- Prophylaxis of uric acid renal stones

Disclaimer: This formulary is for educational purposes only, it should not be used in clinical practice for prescribing.
Prescribing and Safety

Starting dose – 100mg daily after food
Maintenance dose – Mild 100-200mg daily
Moderate 300-600mg daily
Severe 700-900mg daily

Adverse effects:
Important:
- Rash – discontinue allopurinol
- Hypersensitivity reactions including exfoliation, vasculitis, hepatitis and renal impairment
- Hepatotoxicity
- Blood disorders including haemolytic anaemia and leucopenia

Contra-indications and cautions
- Ensure patient is adequately hydrated – fluid intake 2-3 litres/day
- Caution in hepatic and renal impairment and in pregnancy

Interactions
- ACE inhibitors (increased risk of leucopenia and hypersensitivity, especially in renal impairment)
- Azathioprine (increased risk of toxicity) – divide azathioprine dose by 4
- Mercaptopurine (increased risk of toxicity) – divide mercaptopurine dose by 4

Therapeutic drug monitoring

Safety:
Efficacy: Monitor plasma or urinary uric acid concentration to determine dose adjustments; improvement in symptoms, reduced frequency of acute attacks

Patient communication:
Advise patients that they should not stop taking this medication unless told to do so by their doctor. Explain to patients that they should take this medicine with food and plenty of water.

Additional comments:
A prophylactic NSAID (not aspirin) or colchicine should be administered until at least 1 month after hyperuricaemia corrected to avoid precipitating an acute attack.

** Check if patient who presents with gout is on a prescribed a thiazide diuretic

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Antidotes

Naloxone
Naloxone is an opioid receptor antagonist which competes with opioid analgesics for essential receptor sites. It is used in the treatment of opioid overdose to reverse severe respiratory depression and sedation/coma. Naloxone has a short duration of action which is often less than that of the drug taken, particularly methadone which has a very long half-life. Therefore, multiple doses may need to be given. Naloxone is administered by intravenous injection at a dose of 1.2-2.0mg or by continuous intravenous infusion if the ingested drug has a long half-life.

N-acetylcysteine
This drug is used as an antidote to paracetamol overdose. At normal dosage, paracetamol is oxidised to form a highly reactive metabolite which is immediately conjugated with glutathione in the liver and excreted as cysteine and mercaptopurine conjugates. At excessive dosages, stores of glutathione become depleted and the liver is unable to conjugate and deactivate the toxic metabolite. This metabolite accumulates and is responsible for the hepatotoxicity seen in paracetamol overdose.

N-acetylcysteine acts by replenishing stores of glutathione and therefore allowing the toxic metabolite of paracetamol to be safely conjugated and excreted. It is not required in all patients and a treatment nomogram is used to determine whether or not the patient should receive this drug. Plasma paracetamol levels should be urgently measured as soon as 4 hours have elapsed since the overdose. If the levels are above the relevant treatment line on the nomogram, N-acetylcysteine should be given intravenously in the following regimen – initially 150mg/kg over the first 15 minutes then 50mg/kg over the next 4 hours then 100mg/kg over the next 16 hours.

NB. If >8 hours have elapsed and the patient is believed to have taken > 150mg/kg paracetamol, or if there is doubt about timing or the need to treat, N-acetylcysteine should be started immediately while awaiting an urgent plasma paracetamol level.
**Emergency drugs**

**Adenosine**

Intravenous adenosine is useful in the emergency management of supraventricular tachycardia (SVT) for rapid conversion back to sinus rhythm. Its **mechanism of action** is as follows:

**Target:** G protein-coupled adenosine A₁ receptor

**Action:** Agonist

**Effect:** Inhibits adenylyl cyclase enzymes resulting in reduced production of cyclic AMP (cAMP). This promotes opening of adenosine-sensitive potassium channels and increased K⁺ efflux – as a result cells in the atrioventricular node of the heart become hyperpolarised. This slows the rate of rise of the pacemaker potential.

**Overall effect:** Slowed conduction through the AV node resulting in a high degree AV block – this is transient, with the effects of a bolus dose of adenosine lasting only 20-30 seconds.

**Unwanted effects** of adenosine which patients should be warned about beforehand include chest pain, dyspnoea, bronchospasm and nausea. These resolve rapidly as the drug is metabolised and eliminated from plasma. This drug should be avoided in second- and third-degree AV block and in sick sinus syndrome unless the patient has a pacemaker fitted. It should also be avoided in those with decompensated heart failure, severe hypotension and COPD/asthma.

Clinically important **interactions** include:

**Theophylline** – blocks adenosine receptors and so inhibits the action of adenosine

**Dipyridamole** – blocks uptake of adenosine by nucleoside transporters for degradation, therefore potentiating its action and prolonging the adverse effects

**Additional information:**

Patient must be connected to an ECG monitor and resuscitation facilities should be available.

Manoeuvres such as carotid artery massage designed to increase vagal tone should be tried first before adenosine is given (unless contraindicated).
Adrenaline
Adrenaline is an endogenous catecholamine hormone and neurotransmitter in the sympathetic nervous system. It is normally synthesised in the adrenal medulla. Adrenaline’s mode of action is as follows:

**Target:** α and β adrenoceptors

**Action:** Agonist

**Effect:** Activation of α adrenoceptors by adrenaline leads to vascular smooth muscle contraction and peripheral vasoconstriction. Activation of β₁ adrenoceptors leads to increased heart rate and force of contraction (contractility) i.e. it has positive chronotropic and positive inotropic effects. Finally, activation of β₂ adrenoceptors leads to bronchial smooth muscle relaxation and bronchodilatation.

Adrenaline is used in the emergency treatment of:

- Acute anaphylaxis
- Cardiac arrest/cardiopulmonary resuscitation

**Administration:**

**In CPR** – Adrenaline 1 in 10000 should be given at a dose of 1mg by IV injection repeated every 3-5 minutes as necessary – use of a central line is preferred but peripheral lines can also be used if flushed with saline solution first to aid entry into the central circulation. If IV access cannot be obtained during cardiac arrest, the intraosseous route can be considered.

**In anaphylaxis** – Adrenaline 1 in 1000 is given at a dose of 500 micrograms (less in children under 12 years). The intramuscular route is preferred when giving adrenaline for the treatment of anaphylactic shock. The best site for injection is the outer aspect of the middle third of the thigh. Patients with severe allergies who are considered to be at risk of anaphylaxis should be trained on the self-administration of adrenaline via ‘EpiPen’ and should carry 2 of these pens with them at all times.

An important adverse effect of adrenaline is hypertension with associated risk of cerebral haemorrhage. Other unwanted effects include hyperglycaemia, metabolic acidosis and injection site reactions e.g. tissue necrosis. This drug should be used with caution in patients with pre-existing significant cardiovascular disease, hypertension, diabetes mellitus and hyperthyroidism.

**Important interactions:**

- **MAOIs** – increased risk of hypertensive crisis
- **Beta Blockers** – risk of severe hypertension, particularly when adrenaline is combined with non-cardioselective beta blockers

**Additional information:**

NB. Adrenaline can also be given IV for anaphylaxis in the dilute 1 in 10000 formulation.
**Calcium Gluconate**

Administration of calcium gluconate is the first step in the emergency management of hyperkalaemia.

**Mechanism of action:**

In hyperkalaemia, the resting membrane potential (RMP) becomes less negative which moves it closer to the threshold potential (TP). This means that less of a stimulus is required to generate an action potential in the cardiac myocyte. Calcium gluconate counteracts this by raising the threshold potential and therefore restoring the gap between RMP and TP. This stabilises and protects the cardiac membrane, preventing the development of potentially fatal arrhythmias.

**Administration:** 10mL of 10% calcium gluconate should be given by intravenous infusion over 2-3 minutes.

**Additional information:**

The effects of calcium gluconate are transient, lasting only 30-60 minutes. If improvement does not occur, further doses of 10ml 10% calcium gluconate can be given intravenously every 10 minutes until the ECG normalises.

**NB.** Hypercalcaemia can potentiate digoxin toxicity, therefore patients on this drug should only receive calcium gluconate if their ECG shows absent P waves or widening of the QRS complex.
**Thrombolytics/Fibrinolytics**

Thrombolytics can be used in the emergency management of ST elevation myocardial infarction (STEMI) and have been shown to reduce mortality – they are not suitable for NSTEMI. Other less common uses include acute pulmonary embolism and acute thrombotic stroke. A range of agents are available e.g. streptokinase, reteplase, alteplase.

**Mechanism of action:**

These drugs work by converting plasminogen to its active form plasmin, a serine protease enzyme which degrades fibrin and breaks up the thrombus. This re-opens the occluded coronary artery, restoring blood flow and oxygenation to the cardiac muscle it supplies.

**Choice of drug:**

Fibrinolytics are most effective when administered within 4 hours of an acute MI and are usually given alongside aspirin and a low molecular weight heparin. There is little difference between each of the drugs, although it is important to note that patients who receive streptokinase once may form antibodies against this drug around 4 days after administration. These antibodies block its action and therefore streptokinase should not be used again until at least 1 year has elapsed. Alteplase and reteplase are forms of recombinant tissue plasminogen activator (tPA) which is naturally present in the body as part of the fibrinolytic system. These drugs are not antigenic and so can be used as an alternative to streptokinase in patients who are likely to have formed antibodies.

**Unwanted effects:**

The most important side effect of fibrinolytic drugs is bleeding. This is usually limited to the injection site but there is a risk of GI and intracerebral haemorrhage. Hypotension can occur, particularly with streptokinase, and can usually be managed by elevating the patient’s legs or slowing the rate of infusion. Other adverse effects are linked to reperfusion – in the setting of MI these include arrhythmias and angina, while in thrombotic stroke and PE there is a risk of cerebral and pulmonary oedema respectively.

These drugs should be avoided in those who have undergone recent surgery and in recent trauma. They are also contraindicated in haemorrhagic stroke, aortic dissection, aneurysm, active peptic ulceration, uncontrolled hypertension, oesophageal varices and severe hepatic impairment. Those with coagulation defects should not receive fibrinolytics.

**Additional information:**

Patients should be monitored for signs of bleeding and intracranial haemorrhage. Blood pressure should also be measured.

If severe haemorrhage occurs this can be reversed by administering tranexamic acid, fresh plasma or coagulation factors.
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