MIMS DESK REFERENCE

DRUG-CLASS OVERVIEW

CPD Programme

Drug-Class Overview CPD Programme

Contents

About the Drug-Class Overview tables

The aforementioned Drug-Class Overview tables cover a selection of some of the most commonly prescribed drug classes and give key considerations in a summarized format. A brief description of the mechanism of action and relevant "black box"-type warnings is given for each drug class or sub-classification.

Each specified class is then arranged by the relevant active ingredients and the:

- usual dosage range
- dosage forms available on the South African market
- half-life
- elimination
- therapeutic area according to registered package insert
- metabolism
- drug- or dose-specific warnings

The tables feature registered indications (as per SAHPRA) for each product, and exclude evidence indications outside the local regulatory framework, i.e. off-label use. Off-label use may be beneficial to the patient, but is subject to the prescribing healthcare practitioner's judgement/knowledge/expertise and does not take into account registered indications elsewhere.

The tables are a summary of key factors relating to the specified drug class, and serve as a memory jogger to the healthcare practitioner; they do not provide a comprehensive description of all the features and safety considerations of the class. When in doubt or requiring further information, healthcare practitioners should consult the relevant package insert or pharmaceutical manufacturer.

Angiotensin-converting enzyme (ACE) inhibitors

Mechanism: ACE-inhibitors inhibit angiotensin-converting enzyme (ACE), which is involved in the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent, direct vasoconstrictor effect. The converting enzyme (ACE) is also responsible for the breakdown of bradykinin, a potent vasodilator. Vasodilation occurs as a result of lower vasoconstriction caused by reduced levels of angiotensin II as well as the vasodilating effect of increased bradykinin. ACE-inhibitors furthermore decrease the secretion of aldosterone, resulting in decreased sodium and water retention.[1,4]

Major/"Black box-type" warnings: ACE-inhibitors can cause injury and death to the developing foetus when used in the second and third trimesters of pregnancy. Treatment should be discontinued as soon as possible once pregnancy is detected.
Avoid a combination of an ACE-inhibitor with aliskiren in diabetic patients as this may lead to renal impairment, hypotension and hyperkalaemia.[5]

Generic name	Usual dosage range[1,2]	Dosage forms[2]	Half life[1,3]	Elimination[1,3]	Therapeutic area[1,2]	Metabolism[1,3]
Benazepril	Initial dose: 10 mg once daily. Maintenance: 20-40 mg/day once daily OR as 2 divided doses	Tablets	10-11 hours	Excreted mainly in the urine; 11-12 % is excreted in the bile	• Hypertension	Hepatic to active metabolite via enzymatic hydrolysis
Captopril	Hypertension: Initially 12,5 mg twice daily increased gradually to maintenance dose of 25-50 mg 2-3 times daily. Maximum 150 mg daily. Heart failure: 6,25-12,5 mg 3 times daily, increased gradually to maintenance dose of 25 mg 3 times daily and not to exceed 50 mg 3 times daily.	Tablets	1,9 hours	Urine (95 %) primarily as unchanged drug, the rest as other metabolites	• Hypertension • Heart failure	Hepatic
Cilazapril	2,5-5 mg once daily (initial dose 1,25 mg for first 2 days)	Tablets	9 hours	Urine as cilazaprilat	• Hypertension	Hepatic to cilazaprilat (active)
Enalapril	Essential hypertension: Initially 10-20 mg daily. Maintenance: 20 mg daily. Reno-vascular hypertension: Initially 5 mg or less. Most patients respond to 20 mg daily. Heart failure or asymptomatic left ventricular dysfunction: Initially 2,5 mg daily increased gradually to usual maintenance dose of 20 mg as single dose OR 2 divided doses as tolerated	Tablets	1,3 hours (t½ of metabolite is longer)	Urine (60 %-80 %) and faeces (minor) as enalaprilat and unchanged drug	• Hypertension • Heart failure	Extensively hydrolysed in the liver to enalaprilat (active)
Lisinopril	Hypertension: Initially 10 mg with usual maintenance dose of 20 mg/day as single dose. Maximum 40 mg/day. Congestive heart failure: Initially 2,5 mg once a day. Usual effective dose is 5-20 mg/day as single daily dose. Maximum 35 mg/day. Acute MI: Start treatment within 24 hours of symptom onset. Initially 5 mg, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Reduce dose temporarily in case of hypotension.	Tablets	11-12 hours	Primarily urine (as unchanged drug)	• Hypertension • Heart failure • After acute myocardial infarction in haemodynamically stable patients	Already an active diacid and does not need to be metabolised *in vivo*
Perindopril	Hypertension: 4 mg daily. Increased to 8 mg as single daily dose after 1 month of treatment if required. Congestive heart failure: 2 mg as single dose in morning. May be increased to 4 mg or 8 mg depending on response.	Tablets	1,5-3 hours (Metabolite 25-30 hours)	Urine (predominantly) as unchanged drug and metabolites	• Hypertension • Heart failure	Hepatic (active metabolite)
Quinapril	Hypertension: Initially 10 mg daily titrated if required to a maintenance dose of 20-40 mg/day as single or 2 divided doses (initially 5 mg/day with concomitant diuretic). Congestive heart failure: Initially 5 mg daily titrated if required up to 40 mg/day in 2 divided doses with concomitant diuretic and/or cardiac glycoside therapy.	Tablets	6 hours	Urine (60 %) as metabolite, faeces	• Hypertension • Heart failure	Hepatic, hydrolysed to quinaprilat, the active metabolite

Angiotensin-converting enzyme (ACE) inhibitors (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[2]	Half life[1,3]	Elimination[1,3]	Therapeutic area[1,2]	Metabolism[1,3]
Ramipril	Hypertension: Initially 2,5 mg daily in patients not on a diuretic. Increase to 5-10 mg daily depending on response. Post MI: Initially 2,5 mg twice daily for 2 days 3-10 days after acute MI if heart failure manifests and patient haemodynamically stable. Increase to 5 mg twice daily if well tolerated. If initial dose of 2,5 mg not tolerated initiate with 1,25 mg twice daily increased to 2,5 mg twice daily. Non-diabetic and diabetic nephropathy: Initially 1,25 mg daily. Double according to response at 2-3 week intervals up to maximum 10 mg daily.	Capsules, Tablets	13-17 hours (metabolite)	Urine (60 %) and faeces (40 %) as parent drug and metabolites	• Hypertension • Heart failure • Reduced risk of cardiac mortalities in patients with increased CV risk	Hepatic to the active form, ramiprilat
Trandolapril	Initially: 0,5 mg as single daily dose. Usual maintenance dose: 2-4 mg/day.	Capsules	6-10 hours	Excreted in urine (33 %) and faeces (66 %) mainly as trandolaprilat	Hypertension	Hepatic to the active form, trandolaprilat

References:

1. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
2. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). October 2012 ed. Johannesburg: Times Media; 2012.
3. Leikin JB, Paloucek FP, editors. Poisoning and Toxicology Handbook 4th ed. New York: Informa Healthcare; 2008.
4. Finkel R, Clark MA, Cubeddu LX, editors. Lippincott's illustrated reviews: Pharmacology. 4th ed. Baltimore: Lippincott Wiliams & Wilkens; 2010.
5. Food and Drug Administration. FDA Drug Safety Communications. New warning and contra-indication for blood pressure medicines containing aliskiren (Tektura). 20 April 2012.

Angiotensin II receptor blockers

Mechanism of action: Angiotensin II receptor blockers selectively block the binding of angiotensin II to the AT_1 receptor, resulting in the effects of angiotensin II being limited. This produces arteriolar and venous dilation and blocks aldosterone secretion which lowers blood pressure and decreases salt and water retention. Unlike ACE inhibitors, angiotensin II receptor blockers do not increase bradykinin levels.[2,4]

Major/"Black box"-type warnings: Drugs that act on the angiotensin system can cause injury and death to the developing foetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]
Candesartan	Hypertension: 8-16 mg once daily. Maximum 32 mg/day. Heart failure: Initially 4 mg once daily, titrated up to target dose of 32 mg once daily or highest tolerated dose.	Tablets	5-9 hours	Excreted in urine and bile, mainly as unchanged drug and a small amount of inactive metabolites	• Hypertension • Heart failure	Hydrolysed during absorption from the gastro-intestinal tract to the active form
Eprosartan	Initially 600 mg once daily which may be increased to 800 mg if required once daily or as 2 divided doses.	Tablets	5-9 hours	Excreted in bile and urine, primarily as the unchanged drug	• Hypertension	Not metabolised
Irbesartan	Initially 150 mg once daily, increased if necessary to 300 mg once daily. Hypertension with type 2 diabetes renal disease: Maintenance dose of 300 mg once daily.	Tablets	11-15 hours	Excreted in bile and urine as unchanged drug and metabolites	• Hypertension	Hepatic enzymatic metabolism to active metabolite. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Losartan	Hypertension: 50 mg once daily; May be increased to 100 mg once daily. Patients with intravascular volume depletion to start on 25 mg/day. Renal protection in type 2 diabetes with hypertension and proteinuria: 50-100 mg once daily based on BP response.	Tablets	1,5-2 hours	Urine and faeces via bile as unchanged drug and metabolites	• Hypertension	Hepatic via CYP2C9 Hepatic enzymatic metabolism to active metabolite. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Telmisartan	40 mg once daily; Maximum 80 mg/day	Tablets	24 hours	Excreted in faeces via bile, mainly as unchanged drug.	• Hypertension	Minimally metabolised by conjugation in the liver to form a pharmacologically inactive metabolite
Valsartan	Hypertension: 80-160 mg once daily. Maximum dose 320 mg daily. Heart failure: Initially 40 mg twice daily, titrated up to 80 and 160 mg twice daily to highest dose tolerated. Maximum: 320 mg/day in divided doses.	Tablets	5-9 hours	Excreted via faeces (83 %) and urine (13 %) as unchanged drug	• Hypertension • Heart failure	Not significantly metabolised and is excreted mainly via the bile as unchanged drug

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). October 2012 ed. Johanneburg: Times Media; 2012.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Leikin JB, Paloucek FP, editors. Poisoning and Toxicology Handbook 4th ed. New York: Informa Healthcare; 2008.
4. Finkel R, Clark MA, Cubeddu LX, editors. Lippincott's illustrated reviews: Pharmacology. 4th ed. Baltimore: Lippincott Wiliams & Wilkens; 2010.

Anticoagulants

Vitamin K antagonists: warfarin

Mechanism of action:[2,3] Warfarin inhibits the hepatic vitamin K-dependent synthesis of coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S.

Major/"Black box"-type warnings:[2] Warfarin can cause major or fatal bleeding. All patients must have regular INR monitoring.[2] Concomitant medication, dietary changes, and other factors affect INR levels achieved with warfarin

Generic name	Dose range[1-3]	Dosage form[1,3]	Half life* (hours)[2,3]	Elimination[2,3]	Therapeutic area[1-3]	Metabolism[2,3,6]
Warfarin	**Adult:** 2-10 mg daily. The dosage must be individualised based on clinical findings and prothrombin time ratio or international normalised ratio (INR).	Tablets	40 hours The half-life of the R-enantiomer ranges from 37-89 hours and the half-life of the S-enantiomer ranges from 21-43 hours.[2] (INR testing after dose adjustment is therefore only valid after 7 days.)	92 % excreted in the urine mainly as metabolites and to a lesser extent in the faeces.	• Prevention and control of thromboembolism.	Warfarin is metabolised in the liver primarily by the cytochrome P450 hepatic microsomal enzyme system. Any drugs that inhibit or induce hepatic microsomal enzymes may affect warfarin metabolism, increasing or decreasing the warfarin plasma concentration and therefore INR value.

Heparin and low-molecular-weight heparins

Mechanism of action:[2,3] Heparin potentiates the inhibitory effect of antithrombin III on the activated forms of clotting factors IX, X, XI, XII and thrombin.

Major/"Black box"-type warning:
Heparin: Haemorrhage, monitor PTT regularly
LMWH: Spinal or epidural haematomas; Risks of increased bleeding; Thrombocytopaenia

Generic name	Dose range[1-3]	Dosage form[1,3]	Half life* (hours)[2,3]	Elimination[2,3]	Therapeutic area[1-3]	Metabolism[2,3,6]
Heparin	**Adult:** I/V - Initial bolus 5 000 IU Subsequent doses determined by partial thromboplastin time (or clotting time in test tube). Usually: 5 000-10 000 IU every 4-6 hours or by IV infusion 30 000-35 000 IU daily. S/C - 5 000 IU every 8-12 hours. **Paediatric dose:**[3] IV: Initial dose 50 IU/kg then 100 IU/kg every 4-6 hours.	Injection	1 to 6 hours (average 1,5 hours)	Inactive metabolites are excreted in the urine.	• Prophylaxis and treatment of thromboembolism.	Metabolised in the liver by phase II mechanisms
Fondaparinux	2,5 mg daily as prophylaxis or 7,5 mg/day as treatment	Injection	13 to 21 hours	50 % to 77 % is renally excreted in the active form	• Acute DVT; • Prophylaxis for post-operative deep vein thrombosis (Hip or knee repair or replacement, Abdominal surgery); • Acute pulmonary embolism	*In vivo* metabolism of fondaparinux has not been investigated since most of the administered dose is eliminated unchanged in urine in individuals with normal kidney function.
Enoxaparin	DVT prophylaxis: 40 mg daily for 7-10 days. DVT treatment: 1 mg/kg 12 hourly for 5-10 days once anticoagulation is established. Unstable angina: 1 mg/kg 12 hourly with aspirin minimum duration of therapy, 2 days	Injection	3 to 6 hours	Renal via glomerular filtration	• Post-operative DVT prevention; • DVT treatment; • Prevention of ischaemic complications	Metabolised in the liver by phase II mechanisms
Dalteparin	DVT prophylaxis post surgery: 2 500 IU to 5 000 IU once daily for 5-7 days. Treatment of DVT: 200 IU/kg/day (Maximum 18 000 IU/day). Unstable angina: 120 IU/kg twice daily (maximum 10 000 IU/12 hours)	Injection	3 to 5 hours[2]	Renal excretion	• Prevention of DVT: Abdominal, Gynaecological, Orthopaedic, hip replacement surgery; • Treatment of DVT; • Unstable angina	Unknown

Anticoagulants (continued)

Generic name	Dose range[1-3]	Dosage form[1,3]	Half life* (hours)[2,3]	Elimination[2,3]	Therapeutic area[1-3]	Metabolism[2,3,6]
Nadroparin	DVT prophylaxis: Abdominal surgery: 2850 IU AXa,* 2 hours before surgery, repeat 8 hours post surgery, then once daily for at least 7 days. Hip/Knee replacement: First dose 12 hours before surgery and 12 hours post surgery; Day 1-3: 38 IU AXa*/kg then 57 IU AXa*/kg from day 4 for at least 10 days. Treatment of DVT given 12 hourly for 10 days (weight-dependent): < 50 kg: 0,4 ml 50-59 kg: 0,5 ml 60-69 kg: 0,6 ml 70-79 kg: 0,7 ml 80-89 kg; 0,8 ml *AXa = antifactor Xa activity unit	Injection[1,3]	2 to 11,2 hours	Excreted by non-saturable renal mechanism	• Prevention of DVT: Abdominal surgery: Hip or knee replacement surgery; • Treatment of DVT	Metabolised in the liver by phase II mechanisms

Platelet inhibitors

Mechanism of action:[2] The active metabolite of thienopyridine contains a thiol group that binds to a free cysteine(s) on the $P2Y_{12}$ receptor and irreversibly blocks ADP binding and receptor activation, thereby inhibiting platelet activation and aggregation.

Major/"Black box"-type warning:[2] Risk of bleeding and thrombocytopaenia.

Clopidogrel is a CYP2C19 poor metaboliser; increased risk of cardiovascular events; bleeding risk is increased with concomitant use of aspirin, NSAIDs or warfarin and premature discontinuation of therapy may increase risk of cardiovascular events in patients undergoing percutaneous coronary intervention.

Generic name	Dose range[1-3]	Dosage form[1,3]	Half life* (hours)[2,3]	Elimination[2,3]	Therapeutic area[1-3]	Metabolism[2,3,6]
Clopidrogel	75 mg/day[3]	Tablets[3]	6 hours	50 % excreted via kidneys, 46 % excreted in faeces[2]	• Prevention of thromboembolism in coronary artery disease: post-stenting. • Prevention of stroke and myocardial infarction. • Secondary prevention of thromboembolic stroke or TIA. • Antiplatelet therapy in aspirin intolerance.[3]	Clopidogrel is a prodrug that is metabolised by 2 main metabolic pathways. In one pathway cytochromes (CYP2C19, CYP3A, CYP2B6, and CYP1A2) initially oxidize clopidrogrel to 2-oxo-clopidrogel (intermediate metabolite) followed by further metabolism to the thiol derivative (active). In another pathway clopidrogrel is hydrolised via esterases to its carboxylic acid derivative (inactive), which accounts for 85 % of all circulating metabolites.
Prasugrel	**Loading dose:** 60 mg. **Maintenance dose:** 10 mg daily. Patients < 60 kg or > 75 yrs, 60 mg loading dose, then 5 mg/day	Tablets	7 to 8 hours	68 % to 70 % excreted in urine as inactive metabolites; 25 % to 27 % excreted in faeces as inactive metabolites	• Reduction of atherothrombotic events post-stenting	Hydrolysis in the intestine to a thiolactone, followed by formation of an active metabolite which is then further metabolised in the liver to inactive compounds

Anticoagulants (continued)

$P2Y_{12}$ platelet inhibitor

Mechanism of action:[11] Inhibits adenosine diphosphate (ADP) receptors of subtype $P2Y_{12}$ on platelets, preventing signal transduction and platelet activation.

Major/"Black box" type"-warning[11]**: Ticagrelor:** May cause significant and sometimes fatal bleeding; do not use in patients with active pathological bleeding or history of intracranial haemorrhage. If possible, discontinue 5 days prior to surgery and do not start therapy in patients scheduled to undergo urgent coronary artery bypass surgery (CABG). Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgery. If possible, manage bleeding without stopping therapy; stopping therapy increases the risk of cardiovascular events.

Ticagrelor and aspirin: Maintenance dose of aspirin above 100 mg reduces the effectiveness of ticagrelor and should be avoided.

Generic name	Dose range[10,11]	Dosage form[10]	Half life* (hours)	Elimination	Therapeutic area	Metabolism
Ticagrelor	Dose: Initiate with single 180 mg loading dose and continue with 90 mg twice daily. Initial aspirin dose to be followed by 75-150 mg maintenance dose daily. Missed doses: Administer 90 mg at scheduled time. Switching patients from clopidogrel: Administer 1st 90 mg dose 24 hours following last clopidogrel dose	Tablets	~7 hours (ticagrelor) ~9 hours (active metabolite)	58 % faeces; 26 % urine	• Prevention of thrombotic events in patients with acute coronary syndrome including those managed with medication and with PCI and CABG	Hepatic enzyme metabolism mainly by CYP3A4 into the formation of a major active metabolite

Direct thrombin inhibitors

Mechanism of action:[2] Inhibit both free and clot-bound thrombin as well as thrombin-induced platelet aggregation.

Major/"Black box"-type warning:[2,6,8] Risk of epidural or spinal haematoma; Risk of bleeding; Affected by P-glycoprotein inducers; Should not be used to prevent major thromboembolic events in patients with prosthetic heart valves

Generic name	Dose range[1-3]	Dosage form[1,3]	Half life* (hours)[2,3]	Elimination[2,3]	Therapeutic area[1-3]	Metabolism[2,3,6]
Dabigatran	DVT prophylaxis post hip or knee replacement surgery: 110 mg within 1 to 4 hours post surgery, then 220 mg daily for 10 days post major knee surgery or 28 days post hip surgery. Reduce stroke and systemic embolism risk in patients with atrial fibrillation: 150 mg twice daily. Continue therapy life-long Treatment of acute DVT and/or pulmonary embolism: 150 mg twice daily following treatment with a parenteral anticoagulant for at least 5 days. Continue treatment for up to 6 months. Prevention of recurrent DVT and/or pulmonary embolism: 150 mg twice dly. Continue therapy life long dependent on patient risk factors.	Tablets	12 to 17 hours	The active form is excreted in urine	• Prevention of DVT: Hip or knee replacement surgery • To reduce the risk of stroke and systemic embolism in atrial fibrillation • Treatment of acute and prevention of recurrent DVT and or pulmonary embolism.	Non-enzymatic hepatic metabolism

Direct Xa inhibitors

Mechanism of action:[2] Anticoagulation by selective inhibition of factor Xa.

Major/"Black box"-type warning:[2,9] Risk of epidural/spinal haematoma; Risk of bleeding. Discontinuing rivaroxaban without introducing an adequate alternative anticoagulant places non-valvular atrial fibrillation patients at an increased risk of thrombotic events, including stroke

Generic name	Dose range[1-3]	Dosage form[1,3]	Half life* (hours)[2,3]	Elimination[2,3]	Therapeutic area[1-3]	Metabolism[2,3,6]
Rivaroxaban	**10 mg tablets:** DVT prophylaxis post hip or knee replacement surgery: 10 mg within 6 to 10 hours post surgery then 10 mg daily for 2 weeks for major knee surgery and 5 weeks for hip surgery. **15 mg and 20 mg tablets:** SPAF: Recommended dose: 20 mg once daily. Continue for as long as risk factors persist. DVT and pulmonary embolism treatment: Initial 15 mg twice daily for 3 weeks followed by 20 mg once daily for continued treatment and prevention of recurrent DVT and PE. Continue therapy as long as VTE risk persists.	Tablets[1,3]	5 to 9 hours[2]	66 % (36 % unchanged) excreted via kidneys, 28 % excreted in faeces[2]	**10 mg Tablets:** • Prevention of DVT: Hip or knee replacement surgery[1,3] **15 mg and 20 mg Tablets:** • Stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (SPAF) • DVT and pulmonary embolism treatment • Recurrent DVT and pulmonary embolism prevention	The major site of metabolism is in the liver. Oxidative metabolism catalysed by CYP3A4/5 and CYP2J2, and hydrolysis are the mechanisms of metabolism[2]

References:

1. Snyman JR, editor. Monthly Index of Monthly Specialities (MIMS). July 2012 ed. Johannesburg: Times Media; 2012
2. Micromedex® Healthcare Series Vol. 154 expires 12/2012
3. SAMF 2012
4. Goodman and Gilmans. The Pharmacological Basis of Therapeutics
5. Sweetman SC, editor. Martindale, The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
6. Pradaxa Highlights of Prescribing Information. Available from: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf
7. AHFS 2012
8. FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic valves. 2012-12-19. http://www.fda.gov/Drugs/DrugSafety/ucm332912.htm
9. http://www.fda.gov/downloads/Drugs/DrugSafety/Post-marketDrugSafetyInformationforPatientsandProviders/UCM295405.pdf.
10. emims.
11 BRILANTA package insert. Available from http://www1.astrazeneca-us.com/pi/brilinta.pdf.

Antidepressants

Major/"Black box"-type warnings: Antidepressants may increase the risk of suicidal thinking and behaviour in children and adolescents with major depressive disorder (MDD) and other depressive disorders.[3]
It is unclear whether selective serotonin re-uptake inhibitor antidepressants used during pregnancy can cause persistent pulmonary hypertension of the newborn.[6]

Tricyclic antidepressants

Mechanism of action:[2,4] Inhibitors of neuronal re-uptake of noradrenaline and serotonin into presynaptic nerve terminals. By blocking the major route of neurotransmitter removal, concentrations of mono-amines in the synaptic cleft are increased, ultimately resulting in antidepressant effects.

Metabolism:[2,3,4] Hepatic enzymatic metabolism to active metabolite.
Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Amitriptyline	Depression: Adults: 25 mg 3 times daily, which (if necessary) may be increased gradually by increments of 25 mg to maximum 150 mg/day. Elderly: 50 mg/day as single or divided dose. Enuresis: 11-16 years: 25-50 mg at bedtime.	Tablets	9-25 hours	Excreted via urine, mainly as metabolites	• Depression • Adjunct therapy for nocturnal enuresis in children over 11 years	Cardiac side effects: Most agents also block other receptors and may result in anti-cholinergic side effects, sedation or drop in blood pressure
Clomipramine	**Oral:** Depression and obsessive-compulsive disorders: 10-25 mg 2-3 times; may be gradually increased to maximum daily dose of 250 mg if required. Geriatrics: 10 mg daily increased gradually to 30-50 mg/day. Cataplexy associated narcolepsy: Adults: 25-75 mg daily. Obsessive-compulsive syndrome in children > 5 years and adolescents: 25 mg/day increased gradually over first 2 weeks up to daily max of 3 mg/kg or 100 mg (whichever is smallest). Increase gradually thereafter to daily max of 3 mg/kg or 200 mg (whichever is smallest). **Injection:** 25-50 mg IMI daily, increased to max 100-150 mg/day. **IV infusion:** 50-75 mg diluted in isotonic saline or glucose solution once daily over 1,5-3 hours.	Injection, Tablets	20-30 hours	Urine (51-60 %) and faeces via biliary elimination (24-32 %)	• Depression • Cataplexy associated narcolepsy • Obsessive-compulsive disorder in adults and children 5 years and older.	Cardiac side effects: Most agents also block other receptors and may result in anti-cholinergic side effects, sedation or drop in blood pressure
Dothiepin	Depression: 25 mg three times daily initially, gradually increased to 50 mg three times daily if necessary OR 75 mg-150 mg as a single night time dose	Capsules, Tablets	14-24 hours	Urine, mainly in the form of its metabolites; small amounts are also excreted in the faeces	• Depression • Depression associated with anxiety	Increased risk of sudden death in cardiac patients has been reported[7]
Imipramine	Adults: 75-150 mg daily in divided doses or as prescribed. Elderly: Maximum 10-30 mg daily. Children: 6-12 years: 25 mg at bedtime. Over 12 years: 50 mg at bedtime. Geriatrics: Initially 10 mg/day, with maintenance dose of 30-50 mg/day.	Tablets	9-28 hours	Urine (as metabolites)	• Depression • Enuresis • Obsessive-compulsive disorder • Parkinsonism • Chronic alcoholism • Child behavioural disorders	Cardiac side effects: Most agents also block other receptors and may result in anti-cholinergic side effects, sedation or drop in blood pressure
Lofepramine	70-140 mg in divided doses which, after 3 days, may be increased to 140-210 mg per day in divided doses if required. Maintenance dose: 70 mg two times daily during or after meals.	Tablets	5 hours	Urine	• Depression	
Trimipramine	25-125 mg/day	Capsules, Tablets	23 hours	Urine	• Depression • Obsessive-compulsive disorder • Enuresis	Cardiac side effects: Most agents also block other receptors and may result in anti-cholinergic side effects, sedation or drop in blood pressure

Antidepressants (continued)

Mono-amine oxidase inhibitors

Mechanism of action:[2,4] Tranylcypromine forms stable complex with mono-amine oxidase (MAO) enzyme, causing irreversible inactivation. This results in increased stores of noradrenaline, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space. This is believed to cause activation of noradrenaline and serotonin receptors, and indirect antidepressant action. Moclobemide is a reversible MAOI and results in fewer interactions with drugs or foods affecting catecholamine release/metabolism and is therefore better tolerated and the only MAOI in practical use at present.

Metabolism:[2,3,4] Hepatic enzymatic metabolism.
Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Tranylcypromine (non-selective inhibitor)	10 mg twice daily, increased to 10 mg 3 times daily after 2 weeks if necessary	Tablets	2,5 hours	Urine, mainly in the form of metabolites	• Depression	Interactions with other drugs/ food increasing catecholamines may result in hypertensive crisis
Moclobemide (selective inhibitor)	Major depression: 300-600 mg daily in divided doses. Social phobia: 600 mg in two divided doses.	Tablets	2-4 hours	Urine (95 %, as metabolites)	• Depression • Social anxiety disorder	

Selective serotonin re-uptake inhibitors

Mechanism of action:[2,4] Blocks the re-uptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity. It should be noted that selectivity for serotonin re-uptake receptors are dose-dependent and most agents also block the re-uptake of other neurotransmitters such as noradrenaline and dopamine. This may lead to distinct differences in the effect of some molecules.

Metabolism:[2,3,4] Hepatic enzymatic metabolism.
Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Citalopram	Depression: Adults: 20-60 mg as a single daily dose. Elderly: 20 mg daily increased to maximum 30 mg daily depending on individual response. Panic disorder: Initially 10 mg daily, increased to 20 mg daily after 1 week. Dose may be increased further to maximum 40 mg daily as required. Obsessive-compulsive disorder: 20 mg/day as a single dose. Dose may be increased in 20 mg increments to maximum 40 mg/day.	Tablets	36 hours	Liver (85 %), urine	• Depression • Panic disorder • Obsessive-compulsive disorder	May cause dose-dependent QT interval prolongation, which can cause Torsades de Pointes, ventricular tachycardia, and sudden death[5]
Escitalopram	Major depression: 10-20 mg as a single daily dose depending on individual response. Panic disorder: 5 mg as single dose for 1st week before increasing to 10 mg daily. May be increased to maximum 20 mg daily depending on individual response. Social anxiety disorder: 10-20 mg as a single daily dose depending on individual response. Generalised anxiety disorder: 10-20 mg as a single daily dose depending on individual response. Obsessive compulsive disorder: 10-20 mg as a single daily dose depending on individual response.	Tablets	27-32 hours	Urine	• Depression • Generalised anxiety disorder • Panic disorder • Obsessive-compulsive disorder	CNS side effects - mania/ hypomania - seizures
Fluoxetine	Depression: 20 mg once daily, which may be gradually increased up to a maximum of 80 mg daily. Bulimia: 60 mg per day recommended. Obsessive-compulsive disorder: 20-60 mg per day.	Capsules, Tablets, Dispersible tablets	1-3 days (acute use), 4-6 days (chronic use)	Urine	• Depression • Obsessive-compulsive disorder • Bulimia nervosa	GI disorder including haemorrhage and seizures

Antidepressants (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Fluvoxamine	Major depression: 100-200 mg daily up to maximum dose of 300 mg daily. If total daily dose exceeds 150 mg take in 2-3 divided doses. Obsessive-compulsive disorder: 50 mg as single evening dose for 3-4 days, after which dose may be increased in 50 mg increments to maximum dose of 300 mg per day.	Tablets	15 hours	Urine	• Depression • Obsessive-compulsive disorder	CNS side effects GI side effects
Paroxetine	Depression: 20 mg daily which may be gradually increased in 10 mg increments to 50 mg/day if required. Panic disorders: 10 mg daily which may be gradually increased weekly in 10 mg increments to maximum 60 mg/day. Recommended dose is 40 mg daily. Obsessive-compulsive disorder: 20 mg daily which may be gradually increased weekly in 10 mg increments to maximum 60 mg/day. Recommended dose is 40 mg daily. Social phobia: 20-40 mg/day. Generalised anxiety disorder: 20-50 mg/day	Tablets, Controlled-release tablets	21 hours	Urine (64 %); faeces (36 % primarily via bile)	• Depression • Panic disorder • Obsessive-compulsive disorder • Social anxiety disorder • Generalised anxiety disorder	CNS side effects: convulsion serotonin syndrome
Sertraline	Depression: 50 mg daily. May be titrated up in 50 mg increments at 2 week intervals to 150-200 mg. Obsessive-compulsive disorder: Minimum effective dose: 50 mg/day. Doses above 100 mg/day have no additional benefit. Panic disorder: Initially 25 mg/day, increased to 50 mg/day after one week. Minimum recommended effective dose: 50 mg/day.	Tablets	26 hours	Urine and faeces (50:50)	• Depression • Obsessive-compulsive disorder • Social anxiety disorder • Panic disorder	CNS side effects: mania GI side effects

Serotonin and noradrenaline re-uptake inhibitors

Mechanism of action:[2,4] Selective inhibitor of the re-uptake of both serotonin and noradrenaline at usual therapeutic dosages, increasing extracellular concentrations of these neurotransmitters and, therefore, increasing neurotransmission.

Metabolism:[2,3,4] Hepatic enzymatic metabolism.

Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Duloxetine	Depression: 60 mg once daily. Diabetic peripheral neuropathic pain: 60 mg once daily.	Capsules	12 hours	Urine (70 %) Faeces (20 %)	• Depression • Diabetic peripheral neuropathic pain	CVS side effects CNS side effects: vertigo GI side effects
Venlafaxine	75 mg once daily. Increase to 150 mg once daily if necessary. Maximum 375 mg daily (low dosages may result in only serotonin re-uptake inhibition)	Capsules, Tablets	5 hours	Venlafaxine is excreted mainly in the urine, mainly in the form of its metabolites, either free or in conjugated form; about 2 % is excreted in the faeces	• Depression • Generalised anxiety disorder • Social anxiety disorder	CNS side effects: convulsions GI side effects: Nausea and vomiting CVS side effects

Noradrenalinee (and dopamine) re-uptake inhibitors

Mechanism of action

Bupropion:[2,4] Weak blocker of neuronal re-uptake of serotonin and noradrenaline compared with tricyclic antidepressants; it also inhibits the neuronal re-uptake of dopamine.

Reboxetine:[2,4] A selective and potent inhibitor of the re-uptake of noradrenalinee; it also has a very weak effect on serotonin re-uptake.

Metabolism:[2,3,4] Hepatic enzymatic metabolism.

Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Bupropion	150 mg daily as a single daily dose in the morning. Dose may be increased to maximum 300 mg daily in divided doses if required.	Tablets (slow and extended release)	20 hours (controlled-release formulations)	Excreted via urine, mainly as metabolites	• Depression • Smoking cessation	Lowers convulsion threshold and may trigger convulsions/epilepsy

Antidepressants (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Reboxetine	Adults: 4 mg twice daily increased if necessary after 3-4 weeks up to 10 mg daily in divided doses. Elderly: 2 mg twice daily, increased to 6 mg/day after 3 weeks if response inadequate.	Tablets	13 hours	Elimination is mainly via urine (78 %) with 10 % excreted as unchanged drug	• Depression	CNS side effects CVS side effects

Tetracyclic antidepressants

Mechanism of action:[2,4]

Maprotiline: Acts as an antagonist at presynaptic adrenergic (α2) receptors, resulting in increased central noradrenergic and serotonergic activity.

Mianserin: Blocks presynaptic adrenergic (α2) receptors and increases the turnover of brain noradrenalinee. Mianserin is also an antagonist of postsynaptic serotonin receptors in some parts of the brain.

Mirtazapine: Enhances the release of noradrenalinee and, indirectly, serotonin through blockade of central presynaptic adrenergic (α2) receptors. The effects of released serotonin are mediated via 5-HT1 receptors as mirtazapine blocks both 5-HT2 and 5-HT3 receptors.

Metabolism:[2,3,4] Hepatic enzymatic metabolism.

Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Maprotiline	25 mg 1-3 times daily OR 75 mg once a day. Maximum 150 mg/day. Geriatrics: Initially 10 mg 3 times per day OR 25 mg once daily. If necessary may be increased in small increments to 25 mg 3 times daily OR 75 mg once daily	Tablets	27-58 hours (mean 43 hours)	Urine (70 %); Faeces (30 %)	• Depression	
Mianserin	Initially 30-40 mg/day in divided or preferably single dose at night. Maintenance: 30-90 mg (generally 60 mg) daily.	Tablets	6-40 hours	Urine, almost entirely as its metabolites, either free or in conjugated form; some is also found in the faeces	• Depression	CNS side effects: depression convulsions
Mirtazapine	Initially 15 mg/day as single dose at bedtime. May be gradually increased according to clinical response. Effective dosage range: 15-45 mg/day.	Tablets	20-40 hours	Urine (75 %) Faeces (15 %)	• Depression	CNS side effects: seizures

Other

Mechanism of action:[2,4] Trazodone: Weak inhibitor of serotonin re-uptake. Therapeutic benefit is related to ability to block postsynaptic 5-HT2A receptors. With chronic use it may desensitize 5-HT1A.

Metabolism:[2,3,4] Hepatic enzymatic metabolism.

Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings
Trazodone	Adults: Optimal dose: between 300-400 mg/day. Mild anxiety and depression: Recommended starting dose: 100-150 mg/day, if depression is predominant symptom, 300-400 mg/day may be required.	Capsules	5 to 9 hours	Urine, and to a lesser extent, faeces almost entirely as metabolites	• Depression • Mixed anxiety and depression	

Melatonergic antidepressant

Mechanism of action:[9,9] Agomelatine: Agonist at the melatonin 1 and 2 receptors and antagonist at 5-HT_{2C} receptors. It is believed that this duel action is responsible for its antidepressant effect

Metabolism:[10] Hepatic enzymatic metabolism to active metabolite

Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3,10]	Elimination[2,3,10]	Therapeutic area[1,2,10]	Drug-specific warnings
Agomelatine	Optimal dose: Adults: 25 mg/day. If no improvement increase to 50 mg/day	Tablets	1-2 hours	Urine (80 %), mainly as metabolites	• Depression	

Antidepressants (continued)

Other

Mechanism of action:[11] Vortioxetine: Serotonin modulator and stimulator as well as a serotonin reuptake inhibitor enhancing serotonergic activity.
Metabolism:[11] Hepatic enzymatic metabolism to inactive metabolite
Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name	Usual dosage range[1,2,11]	Dosage forms[1]	Half life[2,3,10,11]	Elimination[2,3,10,11]	Therapeutic area[1,2,10,11]	Drug-specific warnings
Vortioxetine	Adults: Initial dose: 10 mg once daily, dose may be increased to a maximum of 20 mg daily or reduced to minimum of 5 mg daily depending on patient's response. Dose increase should be in a period of not less than one week of treatment, if required. Decrease dose for patients who are unable to tolerate higher doses	Tablets	~66 hours	59 % urine; 26 % faeces	• Major depression and relapse risk reduction	Extensively metabolised by hepatic enzymes, mainly CYP2D6. Poor metabolisers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolisers

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS) October 2012 ed. Johannesburg: Times Media; 2012.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Leikin JB, Paloucek FP, editors. Poisoning and Toxicology Handbook 4th ed. New York: Informa Healthcare; 2008.
4. Finkel R, Clark MA, Cubeddu LX, editors. Lippincott's illustrated reviews: Pharmacology. 4th ed. Baltimore: Lippincott Wiliams & Wilkens; 2010.
5. Food and Drug Administration. FDA Drug Safety Communications. http://fda.gov/Drugs/DrugSafety/ucm297391.htm
6. Food and Drug Administration. FDA Drug Safety Communications. http://fda.gov/Drugs/DrugSafety/ucm283375.htm. December 2011.
7. Emims electronic database. Prothiaden. Assessed 21 Jan. 2013.
8. Lôo H, Haleb A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT_{2C} antagonist, in the treatment of major depressive disorder: A placebo-controlled dose range study. *International Clinical Psychopharmacology.* 2002; 17 (5): 239-247.
9. Papp M, Gruca P, Boyer P-A., Mocaë E. Effect of Agomelatine in the Chronic Mild Stress Model of Depression in the Rat. *Neuropsychopharmacology.* 2003; 28: 694-703.
10. Valdoxan® Product information. Available from http://secure.healthlinks.net.au/content/servier/pi.cfm?product=sepvaldx
11. BRINTELLIX full prescription information. Available from: http://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=4b0700c9-b417-4c3a-b36f-de461e125bd3

Anti-diabetic agents

Major/"black box-type" warnings:[10,12]
Thiazolidinediones: May cause or exacerbate congestive heart failure in some patients, observe patients carefully for signs and symptoms of heart failure
Liraglutide: has been found to cause a dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice

Insulin
Mechanism of action:[2,11] Insulin therapy aims to imitate both basal and prandial physiological hormone secretion to achieve near-normal glycaemia.
Metabolism:[2] Insulin is rapidly metabolised in the liver (mainly), followed by the muscle and kidney

Origin/Class[1,2]	Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Short-acting insulins: Include regular insulin and insulin analogues.[11] Rapid acting and short duration of action							
Human, recombinant	Regular insulin	Individualise dose, 15 min before/ after meal Total dose per day: 0,5-1 unit/kg/day Combine with Long-acting/basal insulin analogue	Solution for injection SC/IM/IV	Few minutes	Urine	Diabetes mellitus when insulin required	
Biosynthetic	Insulin Aspart	Immediately before a meal Individualise dose: 0,5-1 unit/kg/day	Solution for injection	81 minutes	Urine	Diabetes mellitus when insulin required	
Human, recombinant	Insulin Glulisine	Administer 15 min before/immediately after meal Individualise dose, 0,5-1 unit/kg/day	Solution for injection SC	42 minutes	Urine	Diabetes mellitus when insulin required	
Human analogue, recombinant	Insulin Lispro	Administer close to meal times/soon after meal Individualise dose, 0,5-1 unit/kg/day	Solution for injection SC/IV	1 hour	Urine	Diabetes mellitus when insulin required	
Duel-acting insulins: Contains both fast and Long-acting insulins							
Human analogue, recombinant	30 % regular, 70 % isophane	Individualise dose, 0,3-1 unit/kg/day	Suspension for injection SC	5-10 hours	Urine	Diabetes mellitus when insulin required	
Human analogue, recombinant	25 % insulin lispro, 75 % isophane/NPH	Administer close to meal times/soon after meal Individualise dose, 0,5-1 unit/kg/day	Suspension for injection SC	N/A	Urine	Diabetes mellitus when insulin required	
Human analogue, recombinant	50 % lispro, 50 % isophane/NPH	Administer close to meal times/soon after meal Individualise dose, 0,5-1 unit/kg/day	Suspension for injection SC	N/A			
Long-acting insulins: Should be used in a regimen with a Short-acting insulin. The Long-acting insulin is used for basal insulin control and rapid-acting insulins for prandial control.[2]							
Human analogue, recombinant	Insulin detemir	Individualise, administer 1-2 times daily Administer evening dose with evening meal/12 hours after morning dose	Solution for injection SC	5-7 hours dose dependent	Urine	Diabetes mellitus when insulin required	Do not administer IV
Human analogue, recombinant	Insulin Glargine	Individualise	Solution for injection SC	30 hours *in vitro* in mammalian reticulocytes	Urine	Diabetes mellitus when insulin required	
Human, recombinant	Zinc suspension of Isophane/NPH insulin	Individualise	Solution for injection SC	13 hours	Urine	Diabetes mellitus when insulin required	

Alpha glucosidase inhibitors
Mechanism of action:[2] Alpha-glucosidase inhibitors such as acarbose delays the breakdown of carbohydrates in the gastro-intestinal tract by inhibiting α-glucosidase
Metabolism:[2] Majority of the drug remains unchanged in the lumen, 35 % of the drug is absorbed in the form of a metabolite

Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Acarbose	50 mg three times a day, directly before meal. May be increased to 100 mg three times a day after 6-8 weeks if response inadequate. Maximum: 200 mg three times a day **To delay progression of type II diabetes mellitus with impaired glucose control:** Initial dose 50 mg a day, escalate to 100 mg three times a day within 3 months	Tablets	Majority of the drug remains unchanged in the gut lumen	Urine and faeces	Type II diabetes mellitus inadequately controlled by diet alone, or on diet and oral hypoglycaemic agents, combined with diet and exercise delays progression of type II diabetes mellitus with confirmed impaired glucose tolerance	

Biguanides
Mechanism of action:[2,11] Metformin decreases peripheral insulin resistance and lowers hepatic glucose output
Metabolism:[2,13] Metformin is excreted unchanged

Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Metformin	**Tablets** Initial dose 500 mg three times a day, gradually increase if necessary to max 2550 mg daily Children > 12 years: Usual starting dose is 500-850 mg daily during or after meals. Dose adjustment should be based on blood glucose after 10-15 days. Maximum recommended dose is 2000 mg in 2-3 divided doses. **Extended release tablets** Starting dose: 500 mg daily, adjust dose after 10-15 days according to blood glucose measurements in 500 mg increments every 10-15 days. Maximum dose 2000 mg once daily with meals. if adequate control not achieved, consider 1000 mg twice daily. If control still not achieved, switch to standard tablets at maximum daily dose of 3000 mg.	Tablets, Extended release (XR) tablets	6,2 hours	Urine	Adults and children > 12 years: Type II diabetes mellitus when diet fails, especially in overweight patients. Alone as initial therapy or in combination with a sulphonylurea or insulin in adults or as monotherapy or in combination with insulin in children > 12 years of age.	Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure

Anti-diabetic agents (continued)

Meglitinides

Mechanism of action:[2,11,14,15] Meglitinides stimulate insulin secretion by the pancreatic ß cells.

Metabolism:[2,13] Meglitinides are metabolised by the hepatic enzyme P450 system. Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Nateglinide	**Monotherapy:** 120 mg 30 minutes before meals **Combination therapy with metformin**: 120 mg 30 minutes before meals, when therapeutic target is close, 60 mg may be sufficient	Tablets	1,5 hours	Primarily urine (83 % of which 16 % is unchanged) followed by faeces	Monotherapy in non-insulin dependent diabetes mellitus not adequately controlled by diet and exercise and if patients have not been chronically treated with other antidiabetic agents. Combination therapy with metformin, when inadequately controlled by metformin	
Repaglinide	Individualise. Initial recommended starting dose: 0,5 mg, allow 1-2 weeks between titration steps. Maximum daily dose: 16 mg **Transfer from other oral hypoglycaemics:** Recommended maximum starting dose: 1 mg before main meal **In combination with metformin:** Administer concomitantly 0,5 mg three times a day	Tablets	1 hour	Primarily faeces as metabolites (90 %) followed by urine	Adjunctive to diet and exercise to lower blood glucose in patients with type II diabetes mellitus. May be combined with metformin when repaglinide monotherapy, metformin monotherapy is inadequate. In combination therapy with insulin in type II diabetes mellitus when control is not adequately achieved on sulphonylueas or repaglinide alone	

Sulphonylureas

Mechanism of action:[2,11,14,15] Sulphonylureas stimulate insulin secretion by the pancreatic ß cells

Metabolism:[2,13] Sulphonylureas are metabolised by the hepatic enzyme P450 system. Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Chlorpropamide	Initial dose 250 mg daily Usual maintenance dose 50-500 mg daily	Tablets	35 hours	Metabolites and unchanged drug excreted in the urine	Mature onset of diabetes mellitus not controlled by diet alone	
Glibenclamide	Initial dose 2,5 mg daily, gradually increase dose if necessary by 2,5 mg increments to 15 mg daily. Doses > 10 mg may be divided into 2 daily doses	Tablets	1,4-1,8 hours	Metabolites excreted in the urine and bile	Adjunctive to poor diet response to lower blood glucose levels in patients with non-insulin dependent type 2 diabetes mellitus	Increased cardiovascular mortality
Gliclazide	**Tablets** Initial dose 40-80 mg daily, gradually increase dose if necessary to 320 mg. Doses > 160 mg may be divided into 2 daily doses **Extended release tablets** Initial dose 30 mg as single dose with breakfast. If fasting blood glucose level not decreased satisfactorily, increase dose progressively to 60 mg, 90 mg or 120 mg daily with 1 month intervals between increments except where blood glucose has not decreased after 15 days, increase at the end of the 2nd week of treatment. Maximum daily dose: 120 mg. Gliclazide replacement therapy: 80 mg gliclazide = 30 mg MR tablet. Other sulphonylurea replacement therapy: During changeover initiate 30 mg daily and increase in increments according to patients' metabolic evolution.	Tablets Extended release (MR/SR) tablets	10 hours	Metabolites excreted in the urine and faeces	Adjunctive to poor diet response to lower blood glucose levels in patients with diabetes mellitus	
Glimepiride	Individualise according to blood glucose level at lowest dose to achieve desired metabolic control. A single daily dose is sufficient to provide metabolic control over 24 hours Initial dose 1 mg once daily taken before 1st main meal of the day, gradually increase dose if necessary by 1 mg increments to 8 mg daily. Improved diabetic controlled is associated with improved insulin sensitivity, allowing for reduced requirements, therefore dose requirements must be considered in time	Tablets	9,2 hours	Metabolites excreted in the urine and faeces	Type II diabetes mellitus inadequately controlled by diet and exercise	

Anti-diabetic agents (continued)

Glipizide	Initial recommended dose 2,5 mg before breakfast or midday meal, gradually increase dose if necessary by 2,5-5 mg increments to 30 mg daily. Doses > 15 mg may be divided into 2 daily doses	Tablets	2-5 hours	Metabolites excreted primarily in the urine (80 %) followed by the faeces	Type II diabetes mellitus inadequately controlled by diet alone	

Thiazolidinediones

Mechanism of action:[2,11,14,15] Pioglitazone is a PPAR-γ and improves peripheral insulin sensitivity by increasing adipose tissue lipogenesis, reducing hepatic fat content and hepatic glucose production.

Metabolism:[2,13] Pioglitazone is metabolised by the hepatic enzyme P450 system. Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Pioglitazone	**Monotherapy:** Initiate at 15 or 30 mg once daily, increase if necessary in increments to a maximum of 45 mg once daily **Combination therapy: Sulphonylureas:** Initiate at 15 or 30 mg once daily in combination with current dose of sulphonylurea. If hypoglycaemic, decrease sulphonylurea dose **Metformin:** Initiate at 15 or 30 mg once daily in combination with current metformin dose **Insulin**: Initiate at 15 or 30 mg once daily in combination with current insulin dose. In case of hypoglycaemia/plasma glucose concentration < 5,5 mmol/L, decrease either the insulin/pioglitazone dose. Further adjustments should be individually based on glucose-lowering response	Tablets	3-7 hours	Metabolites excreted in the urine and bile	Adjunctive to diet and exercise in Type 2 diabetes either as monotherapy or in combination with metformin, a sulphonylurea or insulin when diet and/exercise and a single agent result in inadequate glycaemic control	

DPP-4 antagonists

Mechanism of action:[16,17] DPP-4 antagonists inhibit dipeptidyl peptidase-4 and therefore the breakdown of incretin hormones, increasing insulin synthesis or release and decreasing glucagon levels

Metabolism:[9,13] DPP-4 antagonists are metabolised by the hepatic CYP P450 enzyme system and substrates of P-glycoprotein. Beware of drug interactions involving hepatic enzyme inducers or inhibitors

Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Saxagliptin	Recommended: 5 mg daily	Tablets	2,5 hours Metabolite 3,1 hours	Primarily excreted in the urine followed by faeces	Adjunctive to diet and exercise in type 2 diabetes mellitus. May be combined with metformin, a thiazolinedione or a sulfonylurea	
Sitagliptin	Recommended: 100 mg daily	Tablets	12,4 hours	Primarily excreted in the urine followed by faeces	Adjunctive to diet and exercise in type 2 diabetes mellitus. May be combined with metformin, a PPAR agonist	
Vildagliptin	Recommended: 50 mg daily or 50 mg twice daily	Tablets	1,5 hours	Primarily excreted in the urine followed by faeces	Adjunctive to diet and exercise in type 2 diabetes mellitus as add on therapy in combination with metformin, a sulfonylurea or insulin when adequate glycaemic control not achieved	

GLP-1 agonists

Mechanism of action:[2,9,13] GLP-1 agonists activate GLP-1 receptor, increasing insulin secretion, decreasing glucagon secretion and delaying gastric emptying

Metabolism:[13] Minimally metabolised, the role of the hepatic P450 system is unknown

Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Exenatide	Initial recommended dose 5 µg subcutaneously, administer 60 minutes before 2 main meals of the day, approximately 6 hours or more apart for > 1 month. Thereafter dose may be increased to 10 µg subcutaneously twice daily	Solution for Injection	2,4 hours	Urine	Add-on therapy in type 2 diabetes mellitus inadequately controlled by lifestyle modifications and other oral antidiabetic therapy	
Liraglutide	**Monotherapy:** Initial dose: Administer 0,6 mg subcutaneously for at least 1 week, then increase to 1,2 mg. Based on clinical response and after at least 1 week dose may be increased to 1,8 mg **Combination therapy:** May be added in combination with 1 or more oral antidiabetic agents at unchanged dose, but reduce sulphonylurea dose by approximately half to minimise unacceptable hypoglycaemic risk	Solution for injection	13 hours	Urine and faeces	Add-on therapy in type 2 diabetes mellitus inadequately controlled by lifestyle modifications and other oral antidiabetic therapy	

Anti-diabetic agents (continued)

Oral antidiabetic combinations

See respective previously given Biguanide, Sulphonylurea, and DPP-4 antagonist sections for relevant Mechanism of Action and Metabolism

Origin/Class[1,2]	Generic name[1-3]	Usual dosage range[1,3,4,5,6,8]	Dosage forms[1,3,6]	Half life[2,4,7,9,12,13]	Elimination[2,7,13]	Therapeutic area[1]	Drug-specific warnings[1,3,6,18]
Biguanide, Sulphonylurea	Metformin, Glibenclamide	Individualise components in same ratio where monotherapy with metformin did not result in adequate control. Administer before meal in 1-2 divided doses in the morning and evening. **Diet and exercise alone not adequate:** 250/1,25 mg daily **Inadequate monotherapy control:** 500/2-2,5 mg daily **Substitute from bi-therapy by metformin with insulin-secretagogue:** 500-1000/2,5-5 mg daily according to previous dose of each component Dose may be adjusted every 1-2 weeks according to results. Total daily dose of 2000/20 mg daily not to be exceeded.	Tablets (various dosage strengths available)	See individual drugs	See individual drugs	Initial therapy in type 2 diabetics as adjunctive therapy where diet and exercise alone has not achieved adequate glycaemic control or as 2nd line therapy in type 2 diabetes where diet, exercise and initial sulphonylurea or metformin treatment did not achieve adequate glycaemic control.	
Biguanide, Sulphonylurea	Metformin, Glimepiride	Individualise, initiate lowest effective dose, dose increase dependent on blood glucose level. Administer 500/2 mg 1-2 times daily before or with meals. When switching from combination therapy of glimepiride plus metformin as separate tablets, admininister combination tablet(s) on basis of dose currently taken.	Tablets	See individual drugs	See individual drugs	Adjunctive to diet and exercise in non-insulin depended diabetes mellitus who are well-controlled and stabilised on indivual components in the same ratio where monotherapy with glimepiride or metformin did not result in adequate glycaemic control or replacement of glimepiride and metformin combination therapy.	
Biguanide, DPP-4 antagonist	Metformin Sitagliptin	Individualise according to current regime, efficacy or tolerability not exceeding maximum recommended daily dose of 100 mg sitagliptin. Administer twice daily with meals. Usual dose is 500-1000/50-100 mg. **Switching from co-administration of sitagliptin and metformin:** Base starting dose on current sitagliptin and metformin dose. **Patients inadequately controlled on dual combination therapy with 2 of the following 3 agents (sitagliptin, metformin or a sulphonylurea):** Usual starting dose should provide sitagliptin 50 mg twice daily. Consider patient's glycaemic control level and current metformin dose, when determining metformin starting dose. Patients currently on or initiating a sulphonylurea may require a lower sulphonylurea dose.	Tablets (various dosage strengths available)	See individual drugs	See individual drugs	Diet and exercise adjunctive in type 2 diabetes mellitus patients who are already stabilised with separate sitagliptin and metformin combination at same dose. Diet and exercise adjunctive in combination with a sulphonylurea in type 2 diabetes mellitus inadequately controlled with any 2 of the 3 agents of metformin, sitagliptin or sulphonylurea.	Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure
Biguanide, DPP-4 antagonist	Metformin, Vildagliptin	Recommended starting dose is based on patients' current vildagliptin and/or metformin regimen. Administer with meals Usual dose is 850-1000/50-100 mg. Do not exceed maximum daily dose of vildagliptin 100 mg.	Tablets (various dosage strengths available)	See individual drugs	See individual drugs	Diet and exercise adjunctive in type 2 diabetes mellitus who are already stabilised with separate vildagliptin and metformin combination at the same dose	

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). April 2013 ed. Johannesburg: Times Media; 2013.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Emims electronic database. Prothiaden. Assessed 18 Feb. 14
4. Actraphane. Summary of characteristics. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000427/WC500025433.pdf
5. APIDRA® Highlight of prescribing information. Available from http://products.sanofi.us/apidra/apidra.pdf
6. Snyman JR, editor. MIMS Desk Reference. Volume 46, 2011 ed. Johannesburg: Times Media; 2011.
7. Lantus Scientific discussion. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000284/WC500036075.pdf
8. NovoLog® Insulin aspart (rDNA origin) Injection http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4254b_13 04 KP%20InsulinAspartFDAlabel102005.pdf
9. DrugBank. TMIC. Online database Assessed 5 April
10. AVANDIA® Prescribing information. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143413.pdf
11. Rys P, Pankiewicz O, Lach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: A systematic review. *Diabetes & amp; Metabolism.* 2011:37;190-200.
12. Scientific discussion on Protaphane. European Medicines Agency. 2004. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000442/WC500044216.pdf
13. Epocrates Online. Epocrates. Online database Assessed 5 April 14
14. Tahrani AA, Piya MK, Kennedy A & Barnett AH. Glycaemic control in type 2 diabetes: Targets and new therapies. *Pharmacology & amp; Therapeutics* 125, 328-361 (2010).
15. Sun H, Scott DO. Impact of genetic polymorphisms of cytochrome P450 2 C (CYP2C) enzymes on the drug metabolism and design of antidiabetics. *Chemico-Biological Interactions* 194, 159-167 (2011).
16. Vardarli I. *et al.* Inhibition of DPP-4 with Vildagliptin Improved Insulin Secretion in Response to Oral as well as "Isoglycemic" Intravenous Glucose without Numerically Changing the Incretin Effect in Patients with Type 2 Diabetes. *Journal of Clinical Endocrinology & Metabolism* 96, 945-954 (2011).
17. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus (Review). *Cochrane Database of Systematic Reviews* 3, 1-76 (2009).
18. Highlight of prescribing information JANUMET. Available form http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b91a8d21-1a3b-4abc-85e8-7c2ba906a284

Antimicrobials

Major/"Black-box"-type warnings:

Fluoroquinolones have an increased risk of tendonitis and tendon rupture associated with their use and may exacerbate muscle weakness in patients with myasthenia gravis.[4,7]

High dose and prolonged use of aminoglycosides may lead to nephrotoxicity. Aminoglycoside use may lead to irreversible ototoxicity and other neurotoxic side effects, such as vertigo, numbness, tingling, muscle-twitching and seizures. Other risk factors with aminoglycoside use include concurrent anaesthesia, neuromuscular blockers, or large citrate-anticoagulant blood transfusions.[4]

Hospitalise patients receiving chloramphenicol treatment for observation and haematologic monitoring as serious and fatal blood dyscrasias (including aplastic or hypoplastic anaemia, thrombocytopenia, and granulocytopenia) may occur with short or prolonged treatment; some reports of aplastic anaemia ended in leukaemia; avoid use in trivial infections or where not indicated or when safer alternate treatment exists.[4,8]

Clindamycin and lincomycin treatment may lead to overgrowth of *C. difficile*-associated diarrhoea. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality since these infections can be refractory to antibiotic treatment and may require colectomy. Reserve clindamycin for serious infection where less toxic antibiotics are inappropriate.[4]

Antibacterials

Beta-lactams: Penicillins, cephalosporins, carbapenems

Class indication: Gram-positive and -negative bacterial infections not caused by penicillinase-producing organisms

Mechanism of action:[3,4] Beta-lactams are bactericidal and inhibit cell wall mucopeptide synthesis

Metabolism: Most of the penicillins and cephalosporins are metabolised by the hepatic CYP P450 enzyme system. Beware of drug interactions involving hepatic enzyme inducers or inhibitors. Carbapenems are metabolised by hydrolysis (which does not involve the CYP P450 enzyme system) or the kidney.

Cilastatin, used in combination with imipenem, inhibits the human enzyme dehydropeptidase found in the kidney.[3] By combining imipenem with cilastatin, it prevents the breakdown of imipenem.

Penicillins

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Amoxicillin	Adults and children over 40 kg: 250-500 mg 3 times daily Total daily dose: 750 mg-3 g, maximum recommended dose: 6 g/day **Lyme disease:** Isolated erythaema chronicum migrans: 4 g/day; general manifestation: 6 g/day for minimum of 12 days **Respiratory infections:** 500 mg 8 hourly **Gonorrhoea:** 3 g with 1 g probenecid **Endocarditis prophylaxis:** 2 g 1 hour before procedure ***H. pylori* infections associated with duodenal ulcers:** 750 mg-1 g 2 times daily **Children under 40 kg:** 20-50 mg/kg a day. Maximum recommended dose: 150 mg/kg a day **Lyme disease:** isolated erythema chronicum migrans: 25-50 mg/day; general manifestation: 100 mg/kg a day for minimum of 12 days **Gonorrhoea:** 50 mg/kg (maximum 3 g) with 25 mg/kg probenecid (maximum 1 g) **Endocarditis prophylaxis:** 50 mg/kg 1 hour before procedure **Infants:** 20 mg/kg a day in 3 divided doses LRTI: < 6 kg: 300 mg; 6-8 kg: 600 mg Usual: < 6 kg: 150 mg; 6-8 kg: 300 mg	Tablets Syrup Oral Suspension Paediatric Drops	1,0-1,5 hours Half life is prolonged in neonates	Urine primarily (60-75 % unchanged) Bile	Amoxicillin is indicated in the treatment of infections due to susceptible (ONLY ß-lactamase-negative) isolates of the designated bacteria in the conditions listed below: • Respiratory tract infections • Urinary tract infections • Skin and soft tissue infections • Gastro-intestinal infections • Genitourinary infections • Endocarditis prophylaxis • Combination treatment for *H. pylori* infection • Lyme disease • Gonorrhoea	
Amoxicillin-Clavulanic acid (Co-Amoxiclav)	Administer at the start of meals, Amoxicillin combined with clavulanic acid (co-amoxiclav) is given by mouth in a ratio of amoxicillin 2, 4, 7, or 14 parts to 1 part of clavulanic acid, or intravenously in a ratio of 5 parts of amoxicillin to 1 part of clavulanic acid Doses of the combination, calculated on amoxicillin content, are similar to those for amoxicillin used alone (Clavulanic acid is a beta-lactamase inhibitor)	Tablets Oral Suspension Forte Suspension Injection	1,1 h	Amoxicillin: Urine primarily (60-75 % unchanged) Bile Clavulanate: urine (35-45 % unchanged)	• Upper and lower respiratory tract infections • Skin and soft tissue infections • Urinary tract infections caused by beta-lactamase producing organisms	
Ampicillin	Administer oral dose 1 hour before meals, 2 hours after meals **Adults:** 250-750 mg 6 hourly, severe infections increase dose **Children:** 25-75 % of adult dose, increase in relation to age from infants to 15 years **Mild to moderate infections:** < 1 week: 25-50 mg/kg, 12 hourly. 1-4 weeks: 100-200 mg/kg a day in 3 divided doses. Children: 25-200 mg/kg a day	IV or IM injection Capsules Suspension	1,0-1,5 hours Half life may be prolonged in neonates	Urine (75-90 % unchanged) Bile	• Mixed bacterial infection • Penicillin resistant staphylococci	
Benzathine penicillin	Administer by deep IMI once a month Adults: **Strep pharyngitis:** 1 200 000 U **Syphilis and prophylaxis contacts:** 2 400 000 U **Rheumatic fever recurrence:** 1 200 000 U Children: 600 000-1 200 000 U	IM Injection	30 minutes	Urine	• *Streptococcus* pharyngitis • Uncomplicated erysipeloid • Rheumatic fever prophylaxis • Early or latent syphilis	Cardio-respiratory arrest and death associated with inadvertent IV administration

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Benzyl penicillin	Administer as slow IV infusion at a rate of 500 000 U/minute, where 2 000 000 U or more required **Adults:** 500 000-20 000 000 U daily in divided doses, severe infections 20 000 000 U daily **Children:** 10 000-50 000 U/kg a day in 4 divided doses, severe infections 300 000-400 000 U/kg a day **Neonates:** 50 000 U/kg a day in divided doses, severe infections 50 000-200 000 U/kg a day	IV injection	30 min Half life may be prolonged in neonates	Urine (20 % of oral dose unchanged, 60-90 % of IM dose unchanged)	• Gram-positive aerobes and anaerobes including non beta-lactamase-producing staphylococci, and streptococci • Gram-negative cocci (non beta-lactamase-producing) • Gram-negative bacilli including *Pseudomonas* spp. and Entero-bacteriaceae, are insensitive although some strains of *Proteus mirabilis* and *Escherichia coli* may be inhibited by high concentrations • Gram-negative anaerobes • Other organisms including *Actinomyces* and the spirochaetes, *Borrelia*, *Leptospira*, and *Treponema* spp.	
Cloxacillin	**Injection:** Administer IV infusion slowly Adults: IMI 250 mg 4-6 hourly; IVI: 250-500 mg 4-6 hourly; **IV infusion:** 500 mg, 4-6 hourly. Severe infections double systemic doses Intrapleural/intra-articular: 250-500 mg daily Children: 12,5-25 mg/kg 6 hourly 2-10 years: 50 % adult dose. < 2 years: 25 % adult dose **Oral:** Administer 1 hour before meals Adults: 500 mg 6 hourly. Children: 2-10 years: 250 mg 6 hourly	Injection Capsules	0,5-1 hour Half life is prolonged in neonates	Urine	• Penicillinase producing *Staphylococcus* infections resistant to benzyl penicillin	
Ampicillin, Cloxacillin	**Oral:** Administer 6 hourly Adults and children > 10 years: 500 mg-1 g ampicillin, 500 mg-1 g cloxacillin Children 2-10 years: 250-500 mg ampicillin, 250-500 mg cloxacillin. 0-2 years: 250 mg ampicillin, 250 mg cloxacillin **Injection:** Average adult dose: 2-4 g ampicillin, 2-4 g cloxacillin daily, may be increased in severe infections. Adults and children > 10 years: 500 mg-1 g ampicillin, 500 mg-1 g cloxacillin 4-6 hourly Children: 2-10 years: 250-500 mg ampicillin, 250-500 mg cloxacillin 4-6 hourly. ≤ 2 years: 250 mg ampicillin, 250 mg cloxacillin 4-6 hourly. Neonates: 75 mg ampicillin, 75 mg cloxacillin 8 hourly	Capsules Suspension Injection	See individual drugs	Urine	• Susceptible mixed bacterial infections including penicillin resistant staphylococci (beta-lactamase-producing)	
Flucloxa-cillin	Administer 1 hour before meals Adults: 250 mg 4 times daily Children: 2-10 years: 125 mg, 4 times daily. 2 months-2 years: 62,5 mg, 4 times daily	Capsules Suspension	1 hour Half life is prolonged in neonates	Urine	• G+ infections mainly due to staphylococci resistant to benzyl-penicillin. These include bone and joint infections, endocarditis, pneumonia, skin infections (including soft-tissue infections), and toxic shock syndrome (beta-lactamase-producing)	
Amoxi-cillin, Flucloxa-cillin	Administer 3 times a day, 1 hour before meals. In severe infections the dose may be increased Adults: 500 mg amoxicillin, 500 mg flucloxacillin Children: 2-12 years: 125-250 mg amoxicillin, 125-250 mg flucloxacillin. > 2 years: 62,5-25 mg amoxicillin, 62,5-25 mg flucloxacillin	Capsules Suspension	See individual drugs	Urine	• Susceptible bacterial infections of mixed origin where penicillin resistance to staphylococci implicated (beta-lactamase-producing)	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Phenoxymethylpenicillin	Administer 30 min before meals Adults and children > 12 years: **Streptococcal infections:** 125-500 mg, 4-8 hourly for 10 days **Pneumococcal infections:** 250-500 mg 6 hourly until patients are afebrile for 2 days **Vincents infections:** 250-500 mg, 6-8 hourly **Recurrence prevention after rheumatic fever and chorea:** 125-250 mg 2 times daily on continuous basis Children: Administer 6 hourly. **Streptococcal infections:** Up to 1 year: 60 mg. 1-5 years: 125 mg. 6-12 years: 250 mg	Tablets Oral suspension	0,5-1 hour	Urine	• Penicillin G-sensitive infections similar to benzylpenicillin	
Piperacillin Tazobactam	Administer by slow IV infusion over 30 minutes. Treat 5-14 days and for 48 hours after resolution of clinical symptoms Adults and children > 12 years: Usual: 4 g/500 mg piperacillin-tazobactam 8 hourly **Immunocompromised and neutropenic patients:** 4 g/500 mg piperacillin-tazobactam 6 hourly, combine with aminoglycosides **Nosocomial pneumonia and bacterial infections in neutropenic patients and other severe indicated infections:** 4 g/500 mg piperacillin-tazobactam 6 hourly Children: **Complicated UTI/intra-abdominal/skin and soft tissue infection:** Administer 8 hourly: > 50 kg adult dose including an aminoglycoside **Neutropenic patients 2-12 years with fever possibly due to bacterial infections:** 80 mg/10 mg piperacillin-tazobactam 6 hourly **2-12 years weighing up to 40 kg with complicated intra-abdominal infections:** 100 mg/12,5 mg/kg piperacillin-tazobactam. Maximum 4 g/500 mg piperacillin-tazobactam over 30 minutes	IV Injection	Piperacillin: 0,5-1,5 hours Tazobactam: 0,7-1,2 hours	Piperacillin: urine 68 % (100 % unchanged) and bile Tazobactam: urine primarily (80 % unchanged) and bile	Adults: • *H.influenzae* • Community acquired pneumonia • Skin and soft tissue infections • Gastro-intestinal infections • Genitourinary infections Adults and children under 12 years • Combined with aminoglycosides for bacterial infections in neutropenic patients Children 2-12 years: • Intra-abdominal *E.coli*/ bacteroide infections in hospital	

Cephalosporins

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Cefazolin 1st generation	IV continuous or intermittent infusion or IM administration Adults: 250 mg-1,5 g, 6-8-12 hourly. Severe infection: < 6 g/day In life threatening infections 12 g a day has been used Children: 25-50 mg/kg a day in 3-4 divided doses. Severe infection: increase to 100 mg/kg a day **Peri-operative prophylaxis:** 1 g IV 30 min-1 hour prior to surgery. For procedures > 2 hours, 1 g IV/IM during surgery followed by 1 g IV/IM 6-8 hourly post-operatively for 24 hours	Injection	1,8 hours	Urine primarily (60-80 % unchanged)	• Respiratory tract infections • Genitourinary infections • Bone and joint infections, • Septicaemia • Endocarditis • Peri-/intra and post-operative prophylaxis in abdominal hysterectomy	
Cefepime 1st generation	Administer by slow IV, IM or slow IV of 50-100 ml over approximately 30 minutes. Usual duration of therapy: 7-10 days, longer treatment with more severe infection Adults and children > 12 years: **Mild to moderate complicated or uncomplicated UTI:** 500 mg-1 g IV/IM 12 hourly **Mild to moderate infections including bronchitis, skin and skin structures:** 1 g IV/IM 12 hourly **Severe infections:** 2 g IV 12 hourly **Empiric fever in neutropenic patients:** 2 g IV 8 hourly for 7 days or resolution of neutropenia Children 1 month-12 years: **Pneumonia, UTI and skin structure infections:** > 2 months: < 40 kg: 50 mg/kg 12 hourly for 10 days. Severe infections: 8 hourly dosing schedule **Empiric febrile neutropenia:** > 2 months, < 40 kg: 50 mg/kg 8 hourly for 7-10 days 1-2 months: 30 mg/kg 12 hourly, 8 hourly may be considered Children > 40 kg: recommended adult doses applies Children > 12 years, < 40 kg: Dose for young patients < 40 kg Paediatric maximum dose not to exceed maximum adult recommended dose of 2 g 8 hourly	Injection	1,8 hours	Urine primarily (60-80 % unchanged)	Adults: • Lower respiratory tract infection including nosocomial and communal acquired pneumonia • Acute bacterial exacerbations of chronic bronchitis • Acute bronchitis • Urinary tract infections • Skin and soft tissue infections • Complicated intra-abdominal infections • Empiric monotherapy of febrile neutropenia Children: • Lower respiratory tract infection • Urinary tract infections • Skin and soft tissue infections • Empiric monotherapy of febrile neutropenia	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Cephalexin 1st generation	Adults: 1-4 g/day in divided doses **Otitis media:** 75-100 mg/kg a day in 4 divided doses Children: 25 mg-50 mg/kg a day 6 hourly in divided doses. Dose may be doubled in severe infections	Oral suspension	1 hour	Urine primarily (> 90 % unchanged)	• Respiratory tract infections • Genito-urinary tract infections • Skin infections • Bone infections • Otits media infections • Dental infections	
Cefaclor 2nd generation	Adults and adolescents: Usual dos: 375 mg 12 hourly, dose may be doubled in severe infections Children: 20 mg/kg in divided doses	Tablets Oral Suspension MR Tablets	35-54 minutes	Urine primarily (60-85 % unchanged)	• Respiratory tract infections • Otitis media • Skin and soft tissue infections	
Cefoxitin 2nd generation	Administer IV or IM. Adults: 1-2 g 8 hourly. Severe infections: maximum 3 g 6 hourly **Uncomplicated UTI:** 1 g IM 12 hourly **Uncomplicated gonorrhoea:** Single dose 2 g IM with 1 g oral probenecid **Prophylaxis:** 2 g IV 30 minutes-1 hour pre-operatively, followed by 2 additional dose of 2 g IV/IM 6 hourly not extending 24 hours Children: > 2 years: 20-40 mg/kg 6-8 hourly. Maximum dose in severe infections: 200 mg/kg, total dose < 12 g a day **Prophylaxis:** 30-40 mg/kg 6 hourly	Injection	45-60 min	Urine primarily (85 % unchanged)	• Peritonitis • Intra-abdominal/pelvis infections • Genitourinary infections including uncomplicated gonorrhoea • Septicaemia • Endocarditis • Respiratory tract infections • Bone, joint, skin and soft tissue infections • Post-operative infection prophylaxis	
Cefprozil 2nd generation	Administer over 10 days Adults and children > 12 years: **URTI:** 500 mg/day **LRTI:** 500 mg 12 hourly **Sinusitis:** 250 or 500 mg 12 hourly **Uncomplicated UTI:** 500 mg/day **Skin or skin structure infections:** 250 mg 12 hourly or 500 mg 12-24 hourly Children 1-12 years: **UTI, pharyngitis and tonsillitis:** 7,5 mg/kg 12 hourly **Otitis media:** 15 mg/kg 12 hourly **Skin or skin structure infections:** 20 mg/kg/day single dose **Sinusitis:** 7,5-15 mg/kg 12 hourly	Tablets Suspension	1-1,4 hours	Urine	Mild to moderately severe • Respiratory tract • Skin and soft tissue • Urinary tract infections	
Cefuroxime 2nd generation	**Injection:** Administer by IM, IV or IV infusion Adults: Usual: 750 mg 6-8 hourly. Severe infection: 1,5 g IV 8 hourly **Peri-op.prophylaxis:** 1,5 g IV 1-1,5 hours prior to procedure, supplement with 750 mg IV/IM 8 hourly for 24-48 hours **Cardiac and pulmonary operations:** 1,5 g IV at anaesthesia induction followed by 750 mg-1,5 g 8-12 hourly for 24-48 hours **Gonorrhoea:** 1,5 g IM single dose **Meningitis:** 3 g IV 8 hourly Children > 3 months: Usual dose: 60 mg/kg a day. 30-100 mg/kg a day in 3-4 divided doses **Meningitis:** 200-240 mg/kg a day IV in 3-4 div doses possible to reduce dose after 3 days to 100 mg/kg/day when clinical improvement. Neonates: 100 mg/kg a day, decrease to 50 mg/kg a day when indicated **Tablets:** Administer 30 minutes after food Adults: **Sinusitis, acute and chronic bronchitis:** 250 mg 2 times a day for 7 days **Acute uncomplicated cystitis:** 125 mg for 5-10 days **Lyme disease:** Adults and children > 12 years: 500 mg 2 times a day for 20 days Children: **Otitis Media:** 3 months-2 years: 125 mg 2 times a day. > 2 years: 250 mg 2 times a day for 5-10 days	Injection Tablets Suspension	1,2-1,4 hours Half life is prolonged in neonates	Urine primarily (up to 100 % unchanged)	• Respiratory tract infections • Community acquired pneumonia • Ear-nose-and-throat infections • Urinary tract infections • Skin and soft tissue infections • Burn wound infections • Bone and joint infections • Prophylaxis of peri-operative infections • Meningitis caused by pneumonia, *N.meningitidis* or *H.influenzae* • Lyme disease	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Cefixime 3rd generation	Therapy duration:5-14 days Adults and children > 12 years: 200-400 mg/day single or 2 divided doses **LRTI:** 400 mg/day **URTI:** 200 mg/day single dose, in sinusitis administer for 10-14 days **Uncomplicated UTI:** 200 mg/day single dose **Uncomplicated gonorrhoea:** 400 mg/day single dose	Tablets	3-4 hours	Urine (50 % unchanged)	• Respiratory tract infections • Urinary tract infections • Uncomplicated gonorrhoea	
Cefotaxime 3rd generation	Administer by IM, slow IV injection over 3-5 minutes or IV infusion over 20-60 min Adults: Usual: 2 g/day in 2 divided doses. Severe infection: 3-4 g/day in 2-4 divided doses. Very severe infection: ≤ 12 g/day (do not exceed) ≤ 6 divided doses **Prophylaxis:** 1 g 30-90 minutes pre-operatively **Caesarean section:** 1 g after umbilical cord clamp, 2 further doses 6 and 12 hours later **Gonorrhoea:** Single dose of 1 g Children and infants: 50-100 mg/kg/day in 2-4 doses. In exceptional cases: < 200 mg/kg/day **Neonates:** < 1 week: 50 mg/kg IV 12 hourly. 1-4 weeks: 50 mg/kg IV 8 hourly Infections caused by *Pseudomonas aeruginosa* administer concomitant aminoglycoside	Injection	1 hour Active metabolite Desacetylcefotaxime 1,5 hours Half lives increased in neonates	Urine primarily (20-36 % unchanged)	• Respiratory tract infections • Genitourinary infections • Skin and soft tissue infections • Gastro-intestinal infections • Gonorrhoea • Meningitis in children • Prophylaxis in potential contaminating surgical procedures	
Cefpodoxime 3rd generation	Administer with meals Adults: 100-200 mg 12 hourly **Tonsillitis, pharyngitis and acute bronchitis:** 100 mg 12 hourly **Acute sinusitis, acute exacerbation of chronic bronchitis or pneumonia:** 200 mg 12 hourly Children: Average dose: 8 mg/kg/day administer in 2 doses 12 hourly	Tablets Oral Suspension	2-3 hours	Urine (100 % unchanged)	• Respiratory tract infections	
Ceftazidime 3rd generation	Administer as deep IM/slow IVI or infusion over 30 minutes. **Majority of infections:** 1 g 8 hourly or 2 g 12 hourly Adults: 1-6 g/day in divided doses every 8-12 hours **Fibrocystic adults with pseudomonal lung infections:** High dose of 100-150 mg/kg a day in 3 divided doses Elderly: < 3 g/day Children: > 2 months: 30-100 mg/ kg a day in 2-3 divided doses < 2 months: 25-60 mg/kg 2 times a day **Immunocompromised or fibrocystic children:** up to 50 mg/kg 3 times a day to maximum 6 g/day	Injection	1,9 hours Half life prolonged in neonates	Urine primarily (80-90 % unchanged)	• Severe infection including septicaemia • Bacteraemia • Peritonitis • Infections in immuno--compromised patients • Skin and soft tissue infections • Bone and joint infections • Ear-nose-and-throat infections • Respiratory tract infections • Urinary tract infections • Biliary and abdominal infections	
Ceftriaxone sodium 3rd generation	Administer by IM, IV or IV infusion (over at least 30 minutes) Adults: Adults including elderly and children > 12 years: 1-2 g/day single dose, may be increased to 4 g/day **Bacterial meningitis:** 4 g/day single dose **Gonorrhoea:** 125 mg/day IM single dose **Peri-operative prophylaxis:** 1-2 g 30-90 min prior to surgery Children: Neonates ≤ 2 weeks: 20-50 mg/kg a day single dose, maximum 50 mg/kg Infants and children 2 weeks-12 years: 20-80 mg/kg a day single dose. Adult dose applicable to children > 50 kg **Bacterial meningitis:** (Neonates, infants and children): Initially 100 mg/kg/day single dose (maximum 4 g)	Injection	5,8-8,7 hours	Urine primarily (33-67 % unchanged) and bile or faeces	• Septicaemia • Meningitis in neonates and infants • Intra-abdominal infections • Skin and soft tissue infections • Bone and joint infections • Renal and urinary tract infections • Ear-nose-and-throat infections • Respiratory tract infections, especially pneumonia • Uncomplicated gonorrhoea • Peri-operative infection prophylaxis	

Antimicrobials (continued)

Carbapenems

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Doripenem	500 mg 8 hourly by IV infusion over 1 hour **Nosocomial pneumonia:** for 7-14 days **Complicated intra-abdominal infections:** for 5-14 days **Complicated UTI:** for 10 days	Infusion	~1 hour	Urine 85 % (70 % unchanged) and faeces < 1 %	• Nosocomial pneumonia • Complicated intra-abdominal and • Urinary tract infections	
Etrapenem	Administer as IV infusion over 30 minutes, or IM. Therapy duration 3-14 days Adults and children > 13 years: 1 g/day single dose Children: 3 months-12 years: 15 mg/kg 2 times a day, maximum: 1 g/day	Injection	Adults: 4 hours Children: 2,5 hours	Urine 80 % Faeces 100 %	• Moderate to severe complicated intra-abdominal, urinary tract and skin and soft tissue infections • Community acquired pneumonia • Acute pelvis infections	
Imipenem Cilastatim	Adults > 70 kg: 1-2 g/day imipenem, cilastatin combination in 3-4 divided doses, maximum 4 g or 50 mg/kg/day **Cystic fibrosis patients:** Up to 90 mg/kg/day imipenem, cilastatin combination in divided doses maximum 4 g/day **Prophylaxis:** 1 g IV imipenem, cilastatin combination on anaesthesia induction followed by 1 g 3 hours later, a further 500 mg 8 and 16 hours after induction Children: > 40 kg: Adult dose. < 40 kg: 15 mg/kg imipenem, cilastatin combination 6 hourly, maximum 2 g/day	Injection	1 hour (J)	Urine	• Intra-abdominal infections • Lower respiratory tract infections • Septicaemia • Genitourinary infections • Bone and joint infections • Skin and soft tissue infections • Endocarditis • Mixed infections • Prophylaxis after colorectal surgery	
Meropenem	Administer as IV bolus injection over 5 minutes or infusion over 15-30 minutes Adults: 500 mg-1 g 8 hourly **Febrile episode in neutropenic patients:** 1 g 8 hourly **Meningitis:** 2 g 8 hourly Children: Children > 50 kg: Adult dose. 3 months-12 years: 10-40 mg/kg 8 hourly **Meningitis:** 40 mg/kg 8 hourly	Injection	1 hour	Urine (70 % unchanged)	• Single or multiple suspected bacterial infections • Empiric therapy prior to identification of causative organism	

Macrolides

Mechanism of action:[3,4] Macrolides binds to 50S ribosomal subunit, inhibiting protein synthesis. Their ability to be bacteriostatic or bactericidal is concentration and micro-organism dependent

Metabolism:[3,4] Most of the macrolides are somewhat metabolised by the hepatic CYP P450 enzyme system. Beware of drug interactions involving hepatic enzyme inducers or inhibitors. Most macrolides are P-glycoprotein inhibitors

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Azithromycin	**Oral:** Adults and children > 45 kg: 500 mg/day for 3 days Dosage regime over 5 days: 500 mg on day 1, then 250 mg/day on days 2-5 **Chlamydia trachomatis/N gonorrhoea:** 1 g/day single dose Paediatric: Children under 45 kg: Children 1 year and older: Total dose: 30 mg/kg given as single daily dose of 10 mg/kg for 3 days. > 45 kg: as per adults **Injection:** Administer as IV infusion. 1 mg/ml infused over 3 hours and 2 mg/ml concentration unfused over 1 hour. Do not administer as bolus/IMI Adults: 500 mg IV as single dose for 2 days. Convert to oral therapy in accordance with clinical response to complete 7-10 day course	Tablets Capsules Injection Suspension	68 hours	Primarily bile (> 50 % unchanged) followed by Urine (6 % unchanged)	Adults and children older than 1 yr: • Respiratory tract infections including community acquired pneumonia and *Legionellapneumophilia* • Uncomplicated skin and soft tissue infections • Uncomplicated genital Chlamydia trachomatis non multiresistant *N gonorrhoea* Children over 1 year: • Pharyngitis, tonsillitis and otitis media	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Clarithromycin	**Oral:** Adults: 250-500 mg 2 times a day. MR Tablets 500 mg once daily increasing to 1000 mg in severe infections ***H. pylori* eradication:** 500 mg 2 times a day in combination with appropriate antibiotic and acidity lowering agent for 7-10 days **HIV patients with atypical mycobacterial infections:** 500 mg 2 times a day in conjunction with other antimycobacterials as long as benefit demonstrated Children: 7,5 mg/kg 2 times daily for 5-10 days. Severe infections: Maximum dose of 500 mg 2 times daily **Injection:** Safety in children not established Adults: Recommended dose: 1 g daily divided into 2 equal doses, each dose infused over 60 minutes. Limit IV therapy up to 2-5 days for the very ill, change to oral therapy as soon as possible	Tablets Injection MR/XL Tablets Suspension	Clarithromycin: 3-4 hours in 250 mg 12 hourly and 5-7 hours in 500 mg 8-12 hourly Active metabolite 14-hydroxyclarithromycin: 5-6 hours with 250 mg 12 hourly and 7-9 hours with 500 mg 8-12 hourly	Primarily urine (20-40 % unchanged) followed by faeces	• Respiratory tract infections • Skin and soft tissue infections • *H. pylori* eradication in combination with proton-pump inhibitors and other antibiotics • Disseminated and localised *Mycobacterium avium* • *Mycobacterium intracellulare* infection in HIV-positive patients in conjunction with other antimycobacterials	
Erythromycin	**Oral:** Adults: Usually 250-500 mg 6 hourly, may increase 1,5 g-4 g/day according to severity **Mycoplasmic pneumonia infections:** 500 mg 3-4 times a day **Legionnaires disease:** 500 mg-1 g 4 times a day **Chlamydia infections:** 500 mg 6 hourly for at least 7 days **Streptococcal infections:** 250-500 mg 6 hourly for 10 days **Pneumococcal pneumonia:** 250-500 mg 6 hourly **Staphylococcal infections:** 500 mg 6 hourly for 7-10 days **Tetanus:** 500 mg 6 hourly for 10 days **Early syphillis:** 2-4 g/day for 10-15 days **Gonorrhoea:** 500 mg 6 hourly for 5 days **Prophylaxis of bacterial endocarditis:** 1 g 1,5-2 hours pre-operatively, followed by 500 mg 6 hourly for 8 doses or 1 g 1 hour pre-operatively followed by 500 mg single dose 6 hours later **Campylobacterial infections:** 250 mg 4 times a day Children: 30-50 mg/kg a day in divided doses, may be doubled in severe infections. **Topical acne:** Solution: 20 mg/ml. Apply 2 times a day after washing Lotion: 40 mg/30 ml. Reconstitute according to directions, apply to skin of entire face 2 times a day for 10-12 weeks **Injection:** 15-20 mg/kg bm/day (i.e. continuous infusion). 4-5 mg/kg bm 6 hourly (i.e. intermittent administration over 20-60 minutes)	Capsules Suspension Injection Topical Solution Topical Lotion	1,4-2 hours	Bile and urine (5 % unchanged)	• Respiratory tract infections • Acne vulgaris grade II and III • Skin and soft tissue infections • Rheumatic fever and early syphillis prophylaxis in penicillin allergy • Legionnaires disease • Non gonococcal male urethritis and female pelvic infections	
Roxithromycin	150 mg 12 hourly or 300 mg single dose before meals, administer for at least 10 days in ß-haemolytic streptococcal infections	Tablets	8-13 hours	Faeces (mostly unchanged drug)	• Ear-nose-and-throat infections • Respiratory tract infections • Genito urinary infections • Skin and soft tissue infections	
Telithromycin	Adults and children > 12 years: 800 mg/day single dose for 5 days at bedtime For community acquired pneumonia administer for 7-10 days	Tablets	10 hours	Urine (13 %) and Faeces (7 %)	• Community acquired pneumonia in patients over 18 years • Acute exacerbation of chronic bronchitis, acute sinusitis or tonsillitis in patients over 18 years • Tonsillitis and pharyngitis in patients 12 years and older where organisms are resistant to or patient cannot tolerate beta-lactam, macrolide or trimethroprim-sulphamethoxazole antimicrobials	Myasthenia gravis exacerbation, including fatal and life-threatening acute respiratory failure with rapid onset and progression reported; may occur within hours of first telithromycin dose

Antimicrobials (continued)

Aminoglycosides

Mechanism of action:[3,4] Aminoglycosides bind to bacterial 30S ribosomal subunit, inhibiting protein synthesis. Aminoglycosides are bactericidal
Metabolism:[3,4] Aminoglycosides are excreted primarily unchanged
Aminoglycosides are bactericidal in concentration-dependent fashion, i.e. activity and speed of effect is drug-concentration-dependent, whereas side effects such as nephro- and ototoxicity are duration-of-exposure-dependent. This has allowed successful once-daily dosing, i.e. higher peak effect with a putative longer trough effect which translated into lower toxicity with similar or better efficacy

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Amikacin	Adults: Max 20 mg/kg Infants: Max 10 mg/kg	IM injection	2 hours	Urine (100 % unchanged)	Bactericidal against many Gram negative aerobes and some strains of staphylococci	
Gentamicin/ gentamycin	Limit IM administration to 7-10 days, plasma concentration should not to exceed 10 µg/ml Adults: 3-5 mg/kg a day in 3 divided doses 8 hourly **Moderate UTI:** 2 mg/kg a day single dose or 3 doses 8 hourly **Systemic infections:** 2 mg/kg a day single dose or 3 divided doses 8 hourly. Severe infections: 3 mg/kg/day single dose or in 3 equal doses 8 hourly. Life threatening infections: Maximum 5 mg/kg/day as single doses or in 3 divided dose 8 hourly. Dose to be reduced to 3 mg/kg a day as soon as clinically indicated Children: 3-6 mg/kg a day 8 hourly Infants > 1 week: 6 mg/kg a day in 2-3 doses Neonates and infants < 1 week: 6 mg/kg a day in 2 divided doses Same doses may be administered by IV infusion over a period of up to 2 hours. IV administration only recommended when IM route not permitted	Injection Infusion	2-4 hours	Primarily urine (100 % unchanged)	Bactericidal against many Gram negative aerobes and some strains of staphylococci involved in: • Urinary tract infections • Severe systemic infections • Bone and soft tissue infections • Infected burns • Respiratory tract infections • Sepsis • Peritonitis • Biliary tract infections • Eye infections	
Kanamycin	**IM administration:** Adults: usually 15 mg/kg a day in 2-3 doses, maximum 1,5 g/day Children: 5-15 mg/kg a day in divided doses, maximum 600 mg/day for 6 days Neonates: 7,5 mg/kg a day for 1st 3 days of life in 2-4 doses	Injection	2-4 hours	Primarily urine (100 % unchanged)	• Gram negative infections where less toxic anti biotics are not suitable • Gastro-enteritis	
Streptomycin	Administer IM only Adults: Maximum 20 mg/kg Infants: 10 mg/kg	Injection	2,5 hours	Urine	Streptomycin sensitive infections	
Tobramycin	**Injection** Administer IM/IV over 20-60 minutes. Treatment duration 7-10 days Adults: **Serious infections:** 3 mg/kg a day single dose or 3 doses 8 hourly **Life-threatening infections:** Maximum 5 mg/kg/day single dose or 3-4 doses. Reduce to 3 mg/kg/day as soon as clinically indicated Children: 6-7,5 mg/kg/day in 3-4 doses. < 1 week: maximum 4 mg/kg/day in 2 doses 12 hourly **Ophthalmic Preparations** **Solution:** 1-2 drops in eye 4 hourly. **Severe infections:** 2 drops hourly till improvement, then reduce before discontinuing **Ointment: Mild or moderate infections:** 1 cm 2-3 times a day. **Severe infections:** 3-4 hourly till improvement then reduce before discontinuing	Injection Ophthalmic Solution Ophthalmic Ointment	2 hours	Primarily urine (100 % unchanged)	• Potential life-threatening respiratory tract infections • Various nosocomial infections • Complicated and recurrent urinary tract infections • Susceptible external bacterial infections of eye and adnexa	

Tetracyclines

Class indication:[4] Tetracyclines are the drugs of choice in rickettsial infections, ehrlichiosis, trench fever, chlamydial infections including pharyngitis, sinusitis, or pneumonia due to *Chlamydophila pneumonia* and mycoplasmal infections. They are widely used as part of regimens for pelvic inflammatory disease.
Mechanism of action:[3,4] Tetracyclines bind to the 30S and possibly 50S ribosomal subunit(s) preventing the binding of aminoacyl transfer of RNA and therefore inhibition of protein synthesis. Tetracyclines are considered bactericidal
Metabolism:[3,4] Tetracyclines are excreted primarily unchanged except minocycline which appears to undergo some metabolism in the liver

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Doxycycline	Adults: 200 mg/day as a single dose or 100 mg 12 hourly for 1st 24 hours, followed by 100 mg/day. **Severe infections:** 200 mg/day Children: < 50 kg: 4 mg/kg bm immediately then 2 mg/kg bm. **Malaria prophylaxis:** Commence 1-2 days before entry. Continue daily and for 4 weeks after last exposure. Adults and teenagers: 100 mg daily. Children over 8 years: 2 mg/kg once daily up to 100 mg daily. **Trachoma:** 100 mg daily for 40 days **Non-specific urethritis:** 100 mg 2 times daily for 7 days **Acne:** 50 mg daily	Capsules Tablets	17-18 hours	Faeces and urine 30-50 % (primarily unchanged)	• Respiratory tract infections • Rickettsia (Tick bite fever) • Malaria prophylaxis where high level of chloroquine resistance reported and other treatments not tolerated • Acne vulgaris • Brucellosis • Tularaemia • Actinomycosis • Lyme disease • Yaws • Relapsing fever • Leptospirosis	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Lymecycline	Adults: 300 mg 12 hourly, max dose 3 g/day Children: 50 mg/kg a day	Capsules	10 hours	Primarily urine	• Moderate to severe acne • Acute sinusitis • Acute chronic bronchitis exacerbations • *H. pylori* infections • Urogenital infections caused by *Chlamydia trachomatis* • Trachoma • Rickettsial fever • Soft tissue infections	
Minocycline	**Acne:** Initially 50-100 mg 2 times a day. Maintenance: 50 mg 2 times a day Adults: 200 mg initially followed by 100 mg 12 hourly	Capsules Tablets	16 hours	Faeces (34 %) Urine (5-10 %)	• Acne adjunctive treatment • Susceptible organism infections	
Oxytetracycline	Administer 1 hour before or 2 hours after meals **Acne:** 250 mg 12 hourly Adults: 250-500 mg 6 hourly. Maximum: 3 g/day Children: 50 mg/kg a day	Capsules	9 hours	Urine	• Respiratory tract infections • Genito-urinary infections • Rickettsia (Tick bite fever) • Brucellosis • Tularaemia • Actinomycosis • Lyme disease • Yaws • Acne • Leptospirosis	

Chloramphenicols

Mechanism of action:[3,4] Chloramphenicol binds to 50S bacterial ribosomal subunit, inhibiting protein synthesis (dichloroacetic acid derivative) by preventing attachment of aminoacyl transfer RNA to its acceptor site on the ribosome. Chloramphenicol is bacteriostatic but may be bactericidal in susceptible organisms.
Metabolism:[3] Chloramphenicol hydrolysed to inactive drug in the liver, lungs, kidneys, and plasma. As chloramphenicol is inactivated in the liver, it may interact with a vast number of drugs metabolised by the hepatic CYP P450 enzyme system enhancing the effects of coumarin anticoagulants, hypoglycaemics and antiepileptics such as phenytoin. Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Chloramphenicol	**Oral** Adults: 50 mg/kg a day continuing for 2-3 days, after temperature returns to normal, up to maximum 26 g **Certain meningitis cases:** Maximum 100 mg/kg a day may be required **Ophthalmic Preparations:** Ointment: 10 mg/g. Apply a small amount 4 times a day Redidrops: 5 mg/ml. 2-3 drops, 2-3 hourly Solution: 2,5 mg/0,5 ml. Single dose eye drops. Adults and children according to ophthalmologist	Capsules Ointment Redidrops Solution	1,5-4 hours Variable in infants and neonates	Urine (5-15 % unchanged)	• Gram + and gram – susceptible organism infections • Typhoid or paratyphoid fever • Superficial eye and eyelid infections caused by susceptible organisms • Skin infections	

Sulphonamides

Mechanism of action:[4] Sulphonamides are bactericidal as they interfere with the folic acid pathway in the organism. Trimethoprim selectively inhibits dihydrofolate reductase (folate antagonist) and sulfamethoxazole competes with para-aminobenzoic acid (PABA), inhibiting folic acid synthesis
Metabolism:[3] Trimethoprim is excreted primarily unchanged with minimal hepatic metabolism taking place, but sulfamethoxazole is metabolised by the hepatic CYP P450 enzyme system. Trimethoprim-sulphamethoxazole is able to increase the plasma concentration of many drugs such as the coumarin anticoagulants. Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Trimethoprim Sulphamethoxazole	**Oral:** Administer after meals Adults and children > 12 years: trimethoprim 160 mg, sulphamethoxazole 800 mg 2 times a day. For severe cases maximum trimethoprim 240 mg, sulphamethoxazole 1,2 g, 2 times a day. Children: 6-12 years: Trimethoprim 80 mg, sulphamethoxazole 400 mg 2 times a day. 6 months-5 years: Trimethoprim 40 mg, sulphamethoxazole 200 mg 2 times a day. 8 weeks to 5 months: Trimethoprim 20 mg, sulphamethoxazole 200 mg 2 times a day **IV infusion:** Infuse only over 60-90 minutes 80 mg trimethoprim, 400 mg sulphamethoxazole/5 ml. Dilute 5 ml in 125 ml infusion solution Adults and children > 12 years: 10 ml (960 mg) morning and evening. Severe cases: 15 ml (1,44 g) morning and evening for maximum 3 days Children up to 12 years: 2 ml/5 kg bm/day in 2 equal doses. Children < 12 years: Recommended dose 6 mg trimethoprim, 30 mg sulphamethoxazole/kg bm/day. Maximum duration 5 successive days	Tablets Infusion Suspension	Trimethoprim 8-10 hours, prolonged in neonates Sulfamethoxazole: 6-12 hours	Trimethoprim: Primarily urine (unchanged) followed by faeces (4 %) Sulfamethoxazole: Urine (20-40 % unchanged)	• Respiratory tract infections • Genito-urinary infections • Skin and soft tissue infections	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Sulfacetamide sodium	350 mg/3,5 g. Apply small quantity to inner corner of eye 3 times a day	Eye Ointment	Not available	Not available	• Eye and eye socket infections, styes, trachoma	

Quinolones

Mechanism of action:[3,4] Quinolones are bactericidal as they inhibit essential enzymes in the reproduction of bacterial DNA, namely DNA gyrase and topoisomerase IV.
Metabolism:[3,4] Minimally or partially metabolised by hepatic CYP P450 and/or conjugation. Some quinolones are inhibitors of CYP P450 hepatic enzymes

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Ciprofloxacin	**Injection:** Infuse over 60 minutes Adults: Usual dose 100-200 mg IV, 12 hourly. Dose determined by severity, type and sensitivity of infection, age, mass and renal function. Severe complicated infections 400 mg IV, 12 hourly **Cystic fibrosis patients:** 200 mg IV twice a day taking into consideration bm (5-10 mg/kg/day) **Oral** **Tablets and oral suspension:** Adults: 250-750 mg twice a day for 3 days, 5-10 days for acute infections or 4-6 weeks for bone infections **Cystic fibrosis:** 750 mg twice a day taking bm into consideration **UTI:** Acute uncomplicated mild to moderate: 250 mg twice a day. Severe or complicated: 500 mg twice a day **Skin and bone infections:** Mild to moderate: 500 mg twice a day. Severe or complicated: 750 mg twice a day **Infectious diarrhoea:** 500 mg twice a day **Gonorrhoea:** 250 mg single dose, continuing for at least 3 days after signs and symptoms have disappeared **XR Tablets:** **Uncomplicated UTI:** 500 mg once a day for 3 days **Complicated UTI, acute uncomplicated pyelonephritis:** 1000 mg once a day for 7-14 days **Ophthahmic Preparations** Solution: 3 mg/ml **Corneal ulcer/abscess:** 1st day: 2 drops in infected eye every 15 minutes for 6 hours, followed by 2 drops every 30 minutes for the remainder of the day. 2nd day: 2 drops hourly. 3rd-14th day: 2 drops 4 hourly. Dose regime may be extended at discretion of physician. **Bacterial conjunctivitis:** First 2 days: 1-2 drops in conjunctival sac 2 hourly while awake, followed by 1-2 drops 4 hourly while awake until infection resolves. Dose regime may be extended at discretion of physician. Ointment: 3 mg/g **Corneal ulcer/abscesses:** Apply 1,25 cm into conjunctival sac every 1-2 hours around the clock for 2 days then 4 hourly for further 12 days. Dose regime may be extended at discretion of physician **Bacterial conjunctivitis:** Apply 1,25 cm into conjunctival sac/lid margin 3 times a day for 2 days, followed by 2 times a day for further 5 days. Dose regime may be extended at discretion of physician	Injection Tablets XR Tablets Oral Suspension Ophthalmic Solution Ophthalmic Ointment	4 hours	Urine (40-50 % unchanged) followed by faeces	• Lower respiratory tract infections • Urinary tract infections • Skin and soft tissue infections • Gastro-intestinal infections • Bone infections • Gonorrhoea • Corneal ulcer/ abscesses and conjunctivitis caused by susuceptible bacteria	Administer concomitant amino-glycoside with *Pseudomonas Aeruginosa* infections
Gatifloxacin	Day 1 and 2, 1 drop 2 hourly while awake up to 8 times a day. Day 3-7, 1 drop 4 times a day while awake	Eye Drops	4-7 hours	Urine (unchanged)	• Conjunctivitis caused by susceptible bacteria	
Gemifloxacin	**Acute bacterial chronic bronchitis exacerbation and acute sinusitis:** 320 mg a day for 5 days **Community acquired pneumonia:** 320 mg a day for 7 days or 14 days in serious pneumonia **Uncomplicated UTI:** 320 mg a day for 3 days	Tablets	7 hours	Faeces (61 %) followed by Urine (36 %)	• Respiratory tract infections • Urinary tract infection	
Levofloxacin	**Oral and Injection:** Dose determined by severity, type and sensitivity of infection Administer concomitant aminoglycosides in *P.aeruginosa* infections. Infuse over not less than 30 minutes/250 mg **Bronchitis bacterial exacerbation:** 500 mg a day for 5-10 days **Community acquired pneumonia:** 500 mg 1-2 times a day for 10-14 days or 750 mg once daily for 5 days **Sinusitis:** 500 mg a day for 10-14 days **UTI's and acute pyelonephritis: Complicated:** 250 mg a day for 10 days **UTI uncomplicated in women:** 250 mg a day for 3 days **Skin and skin structure infections: Uncomplicated:** 250-500 mg a day for 7-10 days. **Complicated:** 500 mg 1-2 times a day for 10-14 days **Intra-abdominal infections:** 500 mg once daily in combination with anaerobic antibiotics for 10-14 days. In presence of bacteraemia or septicaemia increase dose to 500 mg 2 times daily for 10-14 days **Chronic bacterial prostatitis:** 500 mg once daily for 28 days	Tablets Infusion	6-8 hours	Primarily urine (87 % unchanged)	• Respiratory tract infections including acute exacerbations of chronic bronchitis • Community acquired pneumonia • Sinusitis • Complicated urinary tract infections • Acute pyelonephritis • Uncomplicated urinary tract infections in women • Chronic bacterial prostatitis • Skin and soft tissue infections • Intra-abdominal infections in adults	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Moxifloxacin	**Oral and Injection:** Infuse IV over 60 minutes Adults: **URT and LRT:** 400 mg a day for 5-10 days **Community acquired pneumonia:** 400 mg a day for 7-14 days, initially as IV therapy **Uncomplicated skin and skin structure infections:** 400 mg a day for 7 days **Complicated skin and skin structure infections:** 400 mg a day for 7-21 days, initially as IV **Uncomplicated pelvic inflammatory disease:** 400 mg a day for 14 days **Complicated intra-abdominal infection:** 400 mg a day for 5-14 days initially as IV **Ophthalmic Solution:** 5 mg/ml **Conjunctivitis:** Adults: 1 drop in infected eye 3 times a day for 4 days Children: Safety and efficacy demonstrated in paediatric patients including neonates at same dose as adult	Tablets Injection Eye Drops	12 hours	Urine and faeces	• Mild to moderately severe respiratory tract infections • Complicated and uncomplicated skin and soft tissue infections • Uncomplicated pelvic inflammatory disease • Complicated intra-abdominal infection • Conjunctivitis	
Norfloxacin	**Uncomplicated UTI:** 400 mg 12 hourly for 3 days **Complicated UTI:** 400 mg 12 hourly for 7-10 days **Chronic relapse:** extend treatment to 21 days to 12 weeks	Tablets	3-4 hours	Urine (26-32 % unchanged), followed by bile or faeces	• Urinary tract infections • Pyelitis • Cysto- and pyelonephritis	
Ofloxacin	**Ophthalmic Drops:** 3 mg/ml **Bacterial conjunctivitis:** 1 drop 2-4 hourly for 2 days, followed by 4 times a day for maximum 10 days. **Bacterial corneal ulcer:** 1st 2 days: 1-2 drops every 30 minutes while awake. Awaken approximately 4 and 6 hourly after retiring and instill 1-2 drops. Day 3-7: 1-2 drops hourly while awake. Day 7-9 or till completion: 1-2 drops 4 times a day	Ophthalmic Drops	Bi-phasic half-lives of 4 to 5 and 20 to 25 hours	Urine	• Susceptible external ocular infections • Corneal ulcers	

Other

Lincosamides

Mechanism of action:[4] Lincosamides are considered to be bacteriostatic or bactericidal, depending on susceptibility of the organism and concentration of the drug. Clindamycin binds to the 50S ribosomal subunit and thereby inhibits protein synthesis.

Metabolism:[4] Lincosamides are metabolised by the liver to active and inactive metabolites, but the role of the hepatic CYP P450 system is unknown.

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Clindamycin	**Injection:** Adults: **Moderate to severe infections:** 600-1200 mg/day in 2-3-4 divided doses. **Severe infections:** 1200-2700 mg/day in 2-3-4 divided doses Children > 1 month: 15-40 mg/kg/day in divided doses. In severe infections not < 300 mg a day irrespective of bm **Capsules:** Administer 6 hourly with meals. Adults: **Mild to moderate severe infections:** 150 mg. **Severe infections:** 300-450 mg **Topical:** **Acne Gel:** 1 g/100 g (in combination with benzoyl peroxide 5 g/100 g). Apply gel after washing affected area once daily in the evening. In some cases 4-6 weeks may be required before fully effective. Treatment not to exceed 12 weeks of continuous use. **Acne solution and lotion:** 10 mg/ml. Apply thinly to affected area twice daily. **Vaginal cream:** 20 mg/g. Apply 5 g PV before bedtime for 3-7 consecutive days	Injection Capsules Gel Lotion/ Solution Vaginal Cream	2,4-3 hours	Urine and faeces	• Respiratory tract infections • Bone and joint infections • Anaerobic infections • Severe *Staphylococcus* and *Streptococcus* infections Skin and soft tissue infections • Dental infections • Acute or chronic osteomyelitis and bacteraemia • Bacterial vaginosis • Acne vulgaris	
Daptomycin	**Infusion:** Adults: Do not administer more frequently than once a day. **Complicated skin and skin structure infections:** 4 mg/kg in 0,9 % NaCl over 30 minutes once every 24 hours for 7-14 days. ***S. aureus* bloodstreeam infections including right sided endocarditis:** 6 mg/kg in 0,9 % NaCl over 30 minutes once every 24 hours for minimum 2-6 weeks. Treatment duration may be longer than 14 days in accordance with individual perceived complication risk	Infusion	7 hours	Urine (78 % unchanged) followed by Faeces (6 % unchanged)	• Complicated skin and skin structure infections by susuceptible G+ micro-organisms • *Staphylococcus aureus* bloodstream infections (bacteraemia) including right-sided infective endocarditis	

Antimicrobials (continued)

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Lincomycin	**Injection** Administer IMI: Adults: 600 mg IM 12-24 hourly Children > 1 month: 10 mg/kg 12-24 hourly IV administered as infusion: Adults: 600 mg-1 g 8-12 hourly. Children > 1 month: 10-20 mg/kg/day in 2-3 doses at 8-12 hour intervals	Injection	5,4 hours	Primarily urine followed by bile	• Susceptible gram + infections	

Miscellaneous antibacterials

Mechanism of action:[4]

Fosfomycin: Fosfomycin is a bactericidal agent which inactivates enolpyruvyl transferase and inhibits cell wall synthesis

Linezolid: Linezolid's bactericidal capacity is dependent on the susceptibility of the organism and concentration of the agent. Linezolid binds to 50S ribosomal subunit and inhibits protein synthesis

Sodium fusidate/fusidic acid: Fusidic acid prevents the translocation of peptide subunits and elongation of the peptide chain, thus inhibiting protein synthesis.

Metabolism[4]:

Fosfomycin: Excreted unchanged

Linezolid: Linezolid is oxidised in the liver

Sodium fusidate/fusidic acid: Unknown

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Fosfomycin	**Oral:** Administer 2 hours before next meal Adult women up to 75 yrs: Single 3 g dose Female children > 5 yrs: Single 2 g dose **Transurethral procedure prophylaxis:** Adult men: Single 3 g dose 3 hours before surgery and 2nd 3 g dose 24 hours after surgery	Suspension	5,7 hours	Urine (100 % unchanged) followed by faeces (100 % unchanged)	• Acute uncomplicated *E.coli* sensitive urinary tract infection in females and female children older than 5 yrs • Prophylaxis in diagnostic and surgical transurethral procedures in adult men	
Linezolid	**Injection and Oral:** Infuse solution over 30-120 minutes Adults and adolescents > 12 yrs: **Community acquired and nosocomial pneumonia including concurrent bacteraemia:** 600 mg IV or orally 2 times a day for 10-14 days **Skin and soft tissue infections including concurrent bacteraemia:** 400-600 mg orally/600 mg IV 2 times a day, depending on clinical severity, for 10-14 days **Enterococcal infections including vancomycin-resistant infections and those with concurrent bacteraemia:** 600 mg IV or orally 2 times a day for 14-28 days Children: Neonates-11 yrs: Pre-term neonates < 7 days of age (gestational age < 34 weeks) have lower systemic clearance and larger AUC values than full-term neonates and older infants. By 7 days of age they are similar to full term/older infants **Community acquired and nosocomial pneumonia including concurrent bacteraemia:** 10 mg/kg IV or orally 8 hourly for 10-14 days **Skin and soft tissue infections including concurrent bacteraemia:** 10 mg/kg IV or orally 8 hourly for 10-14 days **Enterococcal infections including vancomycin-resistant infections and those with concurrent bacteraemia:** 10 mg/kg IV or orally 8 hourly for 14-28 days	Tablets Suspension Infusion	4,3-5,4 hours	Urine (30 % unchanged) followed by Faeces	Vancomycin-resistant: • *E.faecium* infections • Nosocomial or community acquired pneumonia caused by *S.aureus* (methicillin-susceptible and resistant strains) or *S.pneumoniae* (including multi-drug resistant strains) • Complicated skin and soft tissue infections caused by *S.aureus* (methicillin-susceptible and resistant strains), *S.pyogenes* or *S.agalactia* • Uncomplicated skin and soft tissue infections caused by *S.aureus* (methicillin-susceptible and resistant strains) and *S.pyogenes*	
Sodium fusidate/ fusidic acid	**Oral:** Adults: Sodium fusidate: Usual: 500 mg 8 hourly, double dose in severe infections **Topical:** 2 % sodium fusidate 1-2 % fusidic acid as a 2 % ointment or medicated dressing applied 3-4 times daily **Ophthalmic Preparation:** All ages: 1 drop 2 times daily continuing for 2 days after eye returns to normal	Tablets Eye Drops	10-15 hours	Primarily in bile as metabolites, followed by urine	• Gram + topical infections, particularly staphylococcus skin infections • *Staphylococcus* infection in combination therapy • Staphylococcal conjunctivitis	

Antimicrobials (continued)

Glycopeptides
Mechanism of action:[4] Glycopeptides interfere with bacterial cell wall synthesis
Metabolism:[3,4] Excreted unchanged

Generic name	Usual dosage range[1-3]	Dosage forms[1,2]	Half life[3,4-6,9]	Elimination[3,4,9]	Therapeutic area[1,3,6]	Drug-specific warnings
Teicoplanin	Administer IM or IV. IV Injection either bolus or 30 minute infusion Adults and elderly patients with normal renal function: **Moderate infections:** Loading dose: 400 mg as single IV injection on 1st day. Maintenance: 200 mg a day administered IV or IM **Severe infections:** Loading dose: 400 mg IV 12 hourly for first 3 doses. Maintenance: 400 mg a day administered IV or IM. Dose of up to 12 mg/kg may be required. Adapt in overweight patients **Prophylaxis in orthopaedic and vascular surgery:** 400 mg as single IV injection at induction of anaesthesia Children from 3 yrs: **Severe infections and neutropenic patients:** 10 mg/kg 12 hourly by IV injection for first 3 doses, followed by 10 mg/kg IV/IM as single daily dose **Moderate infections:** 10 mg/kg 12 hourly by IV injection for 1st 3 doses, thereafter 6 mg/kg IV/IM as single daily dose **CAPD:** Single IV loading dose of 400 mg, then 20 mg/L bag in 1st week, 20 mg/L/ alternate bags in 2nd and 20 mg/L in overnight dwell bag only in 3rd week Oral Administration: **Antibiotic associated diarrhoea:** Administer reconstituted contents of a vial orally 200 mg 2 times daily for 10 days	Injection	60 hours	Urine	• Potential serious Gram + infections including those that cannot be treated with other antimicrobials • Endocarditis • Septicaemia • Osteomyelitis • Respiratory infections • Soft tissue infections • Urinary tract infections • CAPD associated peritonitis • Prophylaxis in orthopaedic or vascular surgery • Antibiotic associated diarrhoea including pseudomembranous colitis	
Vancomycin	**Injection** Adults: Administer 500 mg 6 hourly or 1 g 12 hourly administered IV Maximum administration rate: 500 mg/30 minutes Children: 40 mg/kg a day in divided doses. Infants and neonates: 15 mg/kg initially followed by 10 mg/kg 8-12 hourly (depending on age) **Oral administration:** Dilute dose in 30 ml water. ***C. difficile* pseudomembranous colitis:** Adults: 500 mg-2 g in 3-4 divided doses for 7-10 days Children: 40 mg/kg a day in 3-4 divided doses. Total daily dose not to exceed 2 g	Injection	4-6 hours	Urine (80-90 % unchanged) followed by Faeces (PO route)	• Serious *Staphylococcus* infections in penicillin allergic patients or patients who fail to respond penicillin or cephalosporin therapy • Vancomycin susceptible organism infections resistant to other antimicrobials (methicillin resistant organisms) • Endocarditis • Staphylococcal enterocolitis and *C.difficile* resistant pseudo-membranous colitis	

References:
1. Emims electronic database. Prothiaden. Assessed 5 April 14.
2. Snyman JR, editor. MIMS Desk Reference. Volume 46 2011 ed. Johannesburg: Times Media; 2011.
3. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
4. Epocrates Online. Epocrates. Online database Assessed 5 April 14
5. Essential Medicines and Health Products Information Portal. Available from http://apps.who.int/medicinedocs/en/d/Jh2918e/23.2.html
6. eMC. Actavis. Online database Assessed 5 April 14.
7. Drugs.com Available from: http://www.drugs.com/news/fda-mandates-black-box-warning-some-antibiotics-12915.html
8. Jacoby & Meyers Dangerous Drugs. Available from: http://blackbox.dangerousdrugs.com/black-box-warning-chloramphenicol
9. DrugBank. TMIC. Online database Assessed 5 April

Antifungals

Azole derivatives
Mechanism of action:[3] Alter cell membrane permeability
Metabolism:[3] Azole derivatives are metabolised in the liver. Fluconazole, intraconazole, ketoconazole and voriconazole are **potent** hepatic CYP P450 enzyme inhibitors; co-administration with various agents is contra-indicated. These azoles are able to increase the plasma concentration of many drugs, such as the coumarin anticoagulants. Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Bifonazole	Apply once a day.	Cream Solution	1-2 hours	Urine and faeces	• Skin and mucocutaneous dermatophyte infections	
Clotrimazole	**Vaginal Tablets:** 500 mg once or 100 mg for 6 consecutive days. **Vaginal Cream:** 5 g before retiring for 6 consecutive days or 2 applications a day for 6-12 days. **Candida vulvitis or vulvo vaginitis:** Apply thin application to external genitalae 2-3 times daily for 1-2 weeks. Treat partner to prevent re-infection. **Topical Cream:** 10 mg/g. Apply thinly 2-3 times daily for 3-4 weeks. Continue for 2 weeks after symptoms disappear to prevent relapse. **Lozenges:** Dissolve lozenges slowly in mouth. **Oropharyngeal candidiasis:** 1 troche 5 times a day for 14 days. **Prophylaxis:** 1 troche 3 times a day for chemotherapy duration or until steroid therapy is reduced to maintenance level.	Vaginal Tablets and Cream Topical Cream Lozenges	Unknown	Primarily excreted in bile/faeces, followed by urine	Vaginal Tablets and Cream • Vaginal itching, burning and discharge associated with recurring vaginal candidiasis Cream: • Dermatomycosis due to dermatophytes, moulds and other fungi • Secondary fungal infections Lozenges: • Oropharyngeal candidiasis and reduction of incidence thereof in immunocompromised patients	
Econazole	**Vaginal Cream:** One application on retiring for 2 weeks. **Vaginal Ovules:** 1 Ovule nightly for 3 consecutive nights. **Topical Cream, Powder, Spray:** Apply 2 times a day.	Vaginal Cream Vaginal Ovules Topical Cream Topical Powder Topical Spray	Unknown	Minimally excreted as it is minimally systemically absorbed	Vaginal Cream and Ovules: • Vaginal candidiasis Topical Cream, Powder, Spray: • Dermatomycoses caused by dermatophytes, yeasts, Gram+ bacteria and moulds	
Fluconazole	Adults: **Oral: Vaginal candidiasis:** 150 mg as single dose. **Candida balanitis:** 150 mg as single dose. **Tinea pedis, T. corporis, T. cruris and Candida infects:** 150 mg a week for 2-4 weeks but up to 6 weeks for tinea pedis. **Tinea unguium/onychomycosis:** 150 mg a week until nail regrowth (fingernails: 3-6 months, toenails: 6-12 months). **Cryptococcal meningitis:** 400 mg on 1st day, then 200 mg a day for 6-8 weeks, may be increased to 400 mg a day, depending on response. **Systemic candidiasis:** 1st day 400 mg, then 200 mg daily, duration dependent on clinical response. **IV Infusion: Cryptococcal meningitis:** 400 mg on 1st day, then 200-400 mg a day for 8 weeks depending on clinical response. **Maintenance therapy to prevent cryptococcal meningitis relapse in AIDS patients:** 100-200 mg a day. **Systemic candidiasis:** 1st day 400 mg, then 200 mg a day, increase to 400 mg a day depending on clinical response. **Oropharyngeal candidiasis:** 50-100 mg a day for 7-14 days or longer in severely immunocomprised patients. To prevent relapse in AIDS patients 150 mg a week. **Oesophageal candidiasis:** 200 mg on 1st day followed by 100-200 mg a day with dose of up to 400 mg a day if no clinical response after 14 days. Treat for minimum of 3 weeks and 2 weeks after symptoms have resolved. **Fungal infection prophylaxis with concomitant cytotoxic chemo- or radiotherapy:** 50-400 mg a day based on risk profile, commence therapy several days before anticipated neutropenia and continue for 7 days after neutrophil count rises above 1000 cells per mm^3 **Vaginal candidiasis:** 150 mg as single dose. **Recurrent vaginal candidiasis:** 150 mg as single dose monthly, for 4-12 months. **Candida balanitis:** 150 mg as single dose	Capsules IV infusion	30 hours	Primarily urine (80% unchanged) followed by faeces minimally	• Cryptococcal meningitis and maintenance therapy to prevent relapse of cryptococcal disease in AIDS patients. • Systemic, oropharyngeal and oesophageal candidiasis. • Prevention of fungal infections in patients at risk of such an infection due to to cytotoxic chemo-/radiotherapy. • Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, onychomycosis and dermal Candida infections. • Vaginal candidiasis and prophylaxis of recurrent vaginal candidiasis.	

Antifungals (continued)

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Fluconazole (Continued)	**Dermatomycosis including T. pedis/T. corporis/T. cruris, onychomycosis and dermal Candida infections:** 150 mg as single dose once a week, for 2-4 weeks, tinea pedis up to 6 weeks, tinea unguium continue until infected nail grows out and is replaced. Children > 4 weeks: **Systemic candidiasis and cryptococccal meningitis:** 6-12 mg/kg/day depending on severity, clinical and mycological response. **Oropharyngeal candidiasis:** 6 mg/kg on 1st day followed by 3 mg/kg a day for 2 weeks at least. **Oesophageal candidiasis:** 6 mg/kg on 1st day followed by 3 mg/kg a day with dose of up to 12 mg/kg/ day according to patient's response. Treat for a minimum of 3 weeks and a further 2 weeks after symptom resolution. **Fungal infection prophylaxis with concomitant cytotoxic chemo- or radiotherapy:** 3-12 mg/kg a day depending on extent and duration of induced neutropenia. Children < 2 weeks: Use same mg/kg dose as per paediatric dose but administer every 72 hours. Children 2-4 weeks: Same dose but every 48 hours. Maximum adult daily dose not to be exceeded in children.					
Itraconazole	Adults: **Vulvovaginal candidiasis:** 200 mg 2 times a day for a day or 200 mg once daily for 3 days. **Reducing recurrent vaginal candidiasis:** 200 mg on first day of menstrual cycle for 6 months. **Dermatomycosis:** 100 mg a day for 15 days or 200 mg a day for 7 days **Plantar tinea pedis T. manus:** 100 mg a day for 30 days or 200 mg 2 times a day for 7 days **Fungal keratitis:** 200 mg a day for 21 days **Onychomycosis:** Confirm diagnosis by laboratory tests. Optimum clinical effect reached 1-4 weeks after treatment cessation for skin infections and 6-9 months for nail infections. Continuous treatment: 200 mg a day for 3 months. Pulse treatment: 200 mg 2 times a day for 1 week every 3 weeks **Fingernail infections:** 2 pulse treatments **Toe nail infections:** 3 pulse treatments **Aspergillosis:** 200 mg a day for 2-5 months, increase dose to 200 mg 2 times a day for invasive/disseminating disease. **Candidiasis (excluding vulvovaginal):** 100-200 mg a day for 3 weeks-7 months. Increase dose to 200 mg 2 times a day for invasive/disseminating disease. **Histoplasmosis (excluding meningeal):** 200 mg a day to 200 mg 2 times a day or 400 mg a day for 8 months. **Sporotrichosis:** 100 mg a day for 3 months. **Paracoccidioidomycosis:** 100 mg a day for 6 months. Efficacy of this dose in AIDS patients not available. **Chromomycosis:** 100-200 mg a day for 6 months. **Blastomycosis:** 100 mg a day to 200 mg 2 times a day or 400 mg a day for 6 months	Capsules	40 hours	Urine followed by faeces	• Persistent vulvovaginal candidiasis and dermatomycosis not responding to conventional therapy. • Fungal keratitis. • Onychomycosis caused by dermatophytes and or yeasts. • Systemic asperigillosis, candidiasis, histoplasmosis, sporotrichosis, paracoccidioido-mycosis and blastomycosis.	Should not use in onychomycosis patients if ventricular dysfunction such as congestive heart failure (CHF) or history of CHF or negative inotropic effects; Discontinue if CHF signs and symptoms occur. Potent CYP3A4 inhibitor; co-administration with the following agents are contra-indicated: cisapride, oral midazolam, nisoldipine, felodipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), lovastatin, simvastatin, ergot alkaloids, or methadone; serious cardiovascular events including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred

Antifungals (continued)

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Ketoconazole	Adults: **Tablets:** **Chronic and recurrent vaginal candidiasis unresponsive to topical treatment:** 400 mg a day for 5 days. **All other indications:** 200 mg a day until at least 1 week after symptoms have disappeared and cultures are clear. May be increased to 400 mg if clinical response is insufficient after a reasonable period **Shampoo/Liquid:** **Pityriasis versicolor:** Apply once a day for maximum of 5 days. Apply to affected wet skin area or wet hair, leave for 3-5 min before rinsing. **Seborrhoeic dermatitis:** Apply twice weekly for 2-4 weeks. **Prophylactic seborrhoea dermatitis:** Apply once weekly. **Cream:** Apply once daily till few days after symptoms disappear.	Tablets Shampoo/ Liquid Cream	8 hours	Primarily bile/faeces	Tablets: • Systemic candidiasis • Chronic and recurring vaginal candidiasis unresponsive to topical treatment. • Serious chronic skin, hair and nail infections where topical treatment is ineffective. • Serious GIT mycoses and chronic mucocutaneous candidiasis unresponsive/ resistant to other therapy. • Paracoccidioidomycosis. • Pulmonary oral and/ disseminating histoplasmosis. • Coccidioidomycosis. Shampoo/Liquid: • Infections involving yeast *Pityrosporum.* • Seborrhoeic dermatitis and prophylaxis. Cream: • Skin dermatophyte infections • Cutaneous candidiasis • Tinea versicolor	Weigh up the risk to benefit before commencing treatment. Use ketoconazole tablets only when other effective antifungal treatment is not available or tolerated. Serious cases of hepatotoxicity, including fatal or one's requiring liver transplant, have occurred with oral use, even in patients without hepatic disease risk factors. Inform patients of the risks and monitor closely for QT Prolongation and **Drug interactions.** The following agents are contra-indicated: dofetilide, quinidine, pimozide, or cisapride due to QT prolongation risk. Ketoconazole may increase. drug levels and therefore prolong the QT interval, resulting in life-threatening ventricular dysrhythmias such as torsades de pointes
Miconazole	**Topical Cream:** Apply 2 times a day for 2-4 weeks. **Vaginal Cream:** 1 application nightly for 7 days. A second course may be given. **Oral gel:** Apply after meals 3-4 times a day, continuing for 2 days after infection has cleared. **Fungal stomatitis:** Apply to lesions in evening and leave overnight. Oral candidiasis remove dental prosthetics and brush with gel at night.	Topical Cream Vaginal Cream Oral Gel	24 hours	Little absorption from skin when applied topically	Topical Cream: • Cutaneous Candida albicans candidiasis. • Tinea corporis, tinea cruris, *Trichophyton rubrum* or *T. Mentagrophytes* and *floccosum*, tinea pedis. Oral Gel: • Fungal infections of the mouth • Fungal stomatitis Vaginal Cream: • Recurrent vaginal candidiasis	

Antifungals (continued)

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Posaconazole	**Refractory invasive fungal infections/intolerant patients with refractory invasive fungal infections:** 400 mg 2 times a day. If meal cannot be tolerated, administer 200 mg 4 times a day Therapeutic duration based on severity of underlying disease/immunosuppressed recovery and clinical response. **Coccicioidomycosis:** 400 mg 2 times a day. If meal cannot be tolerated administer 200 mg 4 times a day. Therapeutic duration based on severity of underlying disease/immunosuppressed recovery and clinical response. **Oropharyngeal candidiasis:** Loading dose 200 mg once daily on 1st day followed by 100 mg daily for 13 days. **Refractory oropharyngeal/oesophageal candidiasis:** 400 mg 2 times a day. Therapeutic duration based on severity of underlying disease/immunosuppressed recovery and clinical response. **Invasive fungal infection prophylaxis:** 200 mg 3 times a day. Therapeutic duration based on recovery from neutropenia/immunosuppression.	Oral suspension	35 hours	Urine and faeces	• Oropharyngeal and oesophageal candidiasis. • Candida infections refractory to other appropriate antifungal agents. • Invasive aspergillosis refractory to amphotericin-B. • Fuasariosis/ zygomycosis/ cryptococcosis/ chromoblastomycosis and mycetoma disease refractory to other therapy. • Coccidioidomycosis. • Prophylaxis of invasive fungal infections in patients at high risk of such infections	
Voriconazole	Adults and adolescents > 12 yrs: Treatment duration depends on clinical and mycological response, ranging from 12 weeks to 6 months. Loading dose: **IV:** 6 mg/kg 12 hourly for 24 hours **Oral:** **> 40 kg:** 400 mg 12 hourly for 24 hours **< 40 kg:** 200 mg 12 hourly for 24 hours Maintenance dose: **Breakthrough infection prevention:** **IV:** 3 mg/kg 12 hourly **Oral:** **> 40 kg:** 200 mg 12 hourly. **< 40 kg:** 100 mg 12 hourly **Invasive aspergillosisis, severe *Candida/ Scedosporium* and *Fusarium* infections:** **IV:** 4 mg/kg 12 hourly. **Oral:** **> 40 kg:** 200 mg 12 hourly. **< 40 kg:** 100 mg 12 hourly. **Dosage adjustments:** If response inadequate increase IV maintenance dose to 4 mg/kg 12 hourly and oral maintenance dose to 300 mg 12 hourly. **< 40 kg:** increase oral maintenance dose to 150 mg 12 hourly. Children 2-12 yrs: (limited data available). **Loading dose:** **IV:** 6 mg/kg 12 hourly for 1st 24 hours. **Oral:** 6 mg/kg 12 hourly for 1st 24 hours. **Maintenance dose:** **IV and Oral:** 4 mg/kg 12 hourly	IV Infusion Tablets	Dose-dependent half-life	Primarily urine as metabolites	• Invasive aspergillosisis. • Serious invasive *Candida* spp.(including *C. krusei*) infections. • Serious *Scedosporium* spp. and *Fusarium* spp. fungal infections • Prevention of fungal infection breakthrough in febrile high-risk patients where amphotericin-B cannot be used.	

Polyene antibiotics
Mechanism of action:[3] Polyene antibiotics increase cell membrane permeability by binding to egosterol, a sterol component of the cell membrane, which is essential for fungal cell wall synthesis.
Metabolism:[3,5] Minimally absorbed from GIT and excreted unchanged

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Amphotericin-B	**Amphotericin-B:** **Slow IV infusion:** 0,1 mg/ml, adjust dose to the specific requirement of each patient since tolerance to amphotericin-B IV varies individually. Initial dose: 0,25 mg/kg a day and gradually increased as tolerance permits **Severe infection:** 0,3 mg/kg IV over a period of 2-6 hours **if** patient has good pulmonary and renal function and tolerance to test dose Gradually increase dose to final daily dose of 0,5-0,7 mg/kg Total daily dose: 1,0 mg/kg Total daily dose on alternate days: 1,5 mg/kg	IV infusion	~24 hours	Minimally and slowly in urine (unchanged)	Amphotericin-B: • Potential life-threatening fungal infections. • May be helpful in American Mucocutaneous Leishmania but not drug of choice in primary therapy.	Do not exceed the maximum daily dose of 1,5 mg/kg as it may present in fatal cardiac or cardio-pulmonary arrest

Antifungals (continued)

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Amphotericin-B (Continued)	**Amphotericin-B encapsulated in liposomes** Administer IV infusion over 30-60 minutes. Recommended concentration is 0,20-2,00 mg/ml Only reconstitute with sterile water. Flush existing IV line with 5% dextrose injection before administering and if not feasible, administer through separate line Adults: **Empirical therapy:** 3 mg/kg/day **Systemic fungal infections:** 3-5 mg/kg/day **Cryptococcal meningitis in HIV-infected patients:** 6 mg/kg/day **Visceral Leishmaniasis:** Immuno-competent patients: 3 mg/kg/day on days 1-5, day 14 and day 21. Immuno-compromised patients: 4 mg/kg/day on days 1-5, day 10, day 17, day 24, day 31 and day 38. Children: Calculate dose on same per/kg body weight basis as for adults				Amphotericin-B encapsulated in liposomes: • Presumed fungal infections in febrile neutropenic adults and children unresponsive to anti-bacterial treatment. • Severe systemic and/deep mycoses in adults and children when toxicity (particularly nephrotoxitciy) precluded use of conventional systemic Amphotericin-B or patients resistant to conventional Amphotericin-B. • Visceral leishmaniasis in immunocompetent adults and children and immuncompromised adults. • Cryptococcal meningitis in HIV infected patients.	
Natamycin	1 drop 1-2 hourly in the conjuctival sac. Reduce frequency to 1 drop 6-8 times daily after 3-4 days. Continue for 14-21 days or until resolution of the infection.	Ophthalmic Suspension	N/A	No systemic absorption	• Fungal blepharitis • Conjunctivitis • Keratitis caused by suspectible organism	
Nystatin	**Cream and Ointment:** 100 000 u/g. Apply 2 times a day to infected area **Suspension:** Retain in mouth for as long as possible before swallowing, continue for ≥ 48 hours after symptoms have disappeared Adults, children and infants: 1-2 ml 4 times a day. Severely infected adults and children: 4-6 ml 4 times a day. Newborn prophylaxis: 1 ml daily.	Cream Ointment Suspension	Unknown	Faeces (100 % unchanged)	Cream and Ointment • Cutaneous monilia infections Suspension: • Candidal infections of oral cavity	

Echinocandins
Mechanism of action:[11] Echinocandins inhibit cell wall synthesis by inhibiting the action of the enzyme beta-(1,3)-glucan synthase.
Metabolism:[11] Metabolised slowly in the liver by hydrolysis.

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Caspofungin	**Empirical therapy:** Loading dose: 70 mg as a single dose on day 1, followed by 50 mg a day. Duration based on clinical response, continue until neutropenia resolved. Treat patients found to have fungal infection for minimum of 14 days, continuing for 7 days after neutropenia and symptoms have resolved. If well tolerated daily dose may be increased to 70 mg if adequate response not obtained. **Invasive Candidiasis:** Loading dose: 70 mg on day 1 followed by 50 mg daily thereafter. Duration dictated by clinical and microbiological response. Continue for at least 14 days after last positive culture. **Oesophageal and oropharyngeal candidiasis:** 50 mg daily.	IV infusion	9-11 hours	Urine	• Empirical therapy for presumable fungal infections in febrile neutropenic patients. • Invasive candidiasis, oesophageal and oropharyngeal candidiasis where IV therapy is appropriate.	

Antifungals (continued)

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Caspofungun (Continued)	**Invasive Aspergillosis:** 70 mg as single loading dose on day 1 followed by 50 mg daily thereafter. Duration based on severity of patients underlying disease recovery, immunosuppression and clinical response. Daily dose increase to 70 mg may be considered if no evidence of clinical response and therapy well tolerated.				• Invasive aspergillosis in patients refractory to or intolerant to other therapy including Amphotericin-B, lipid formulation of Amphotericin-B and itraconazole.	

Other
Mechanism of action:[3,5,11]
Amorolfine: Amorolfine interferes with fungal sterol synthesis which is essential for the functioning of fungal cell walls.
Griseofulvin: Griseofulvin is a fungistatic antimicrobial and acts by accumulating in keratin precursor cells, increasing new keratin resistance to fungal invasion.
Terbinafine: Terbinafine inhibits squalene epoxidase which reduces fungal cell membrane ergosterol synthesis.
Tolnaftate: Exact mechanism unknown.
Zinc undecenoate, terpineol, and undecenoic acid: Undecenoic acid and its zinc salt are fungicidal and believed to interfere with the fatty acid biosynthesis of the fungi.
Metabolism:
Amorolfine: N/A
Griseofulvin: Griseofulvin is metabolised by the hepatic CYP P450 enzyme system and a potent inducer thereof. Griseofulvin may therefore interact with a vast number of drugs metabolised by the hepatic CYP P450 enzyme system and decrease their plasma concentration. Beware of drug interactions involving hepatic enzyme inducers or inhibitors.
Terbinafine: Terbinafine is metabolised by the hepatic CYP P450 enzyme system and a potent inhibitor thereof. Terbinafine may therefore interact with a vast number of drugs metabolised by the hepatic CYP P450 enzyme system and increase their plasma concentration. Beware of drug interactions involving hepatic enzyme inducers or inhibitors.
Tolnaftate: N/A
Zinc undecenoate, terpineol and undecenoic acid: N/A

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Amorolfine	File affected nail areas thoroughly and cleanse first with alcohol soaked swab removing remaining lacquer. Apply nail lacquer to entire surface and allow to dry for approximately 3-5 minutes. Apply 1-2 times a week. Continue treatment without interruption, duration of treatment depends on infection intensity, localisation and growth rate of nails. Fingernails: 6 months; Toenails: 9-12 months.	Nail lacquer	N/A	N/A	• Onychomycosis caused by dermatophytes, yeasts and moulds	
Griseofulvin	Adults: 500 mg-1 g daily in 4 divided doses Children: 10 mg/kg bm daily in 4 divided doses. **Severe infections:** 1,5-2 g daily in 4 divided doses for short periods. Continue treatment until infected tissue replaced. Skin and hair: 2-6 months; Fingernails: 6-9 months; Toenails: 1 year.	Tablets	9-24 hours	Urine followed by faeces and sweat	• Mycotic diseases of the skin, hair and nails	
Terbinafine	**Tablets:** Adults and children > 40 kg: 250 mg once daily. Children 20-40 kg: 125 mg once daily. Children < 20 kg (no data available for children under 2 years or < 12 kg): 62,5 mg once daily. **Recommended treatment duration:** **Skin infections:** Tinea pedis: 2-6 weeks Tinea corporis: 2-4 weeks Tinea cruris: 2-4 weeks Cutaneous candidiasis: 2-4 weeks **Hair and scalp infections:** Tinea capitis: 4 weeks Onychomycosis: 6 weeks-3 months **Cream:** Adults and children > 12 yrs: Apply 1-2xdly until infection clears **Spray and Dermgel:** Apply to affected area after cleaning **Tinea corporis, tinea cruris and tinea pedis:** Once a day for 7 days **Pityriasis versicolor:** Twice daily for 7 days **Film forming Solution:** Adults and children > 15 yrs: Wash and dry both feet and hands and then apply even thin layer as single administration once only to both feet even if lesion(s) are only visible on one foot. Apply between and around toes as well as sole and 1,5 cm up sides of foot. Allow to dry. Do not massage in or wash for 24 hrours after application.	Tablets Cream Spray Dermgel Film forming Solution	21 hours	Primarily (75%) urine	Cream, Spray and Dermgel: • Fungal skin infections caused by dermatophyte yeast infections, tinea versicolor Film-forming solution: • Mild to moderately severe tinea pedis Tablets: • Fungal skin infections caused by dermatophytes. • Ringworm and yeast skin infections • Onychomycosis. • Tinea capitis	

Antifungals (continued)

Generic name	Usual dosage range[1-4]	Dosage forms[1-2]	Half life[3,5-8,11]	Elimination[3,5,11,12]	Therapeutic area[1,3,7]	Dose-specific warnings
Tolnaftate	10 mg/g Apply 0,5-1,25 cm twice daily for 2-3 weeks.	Cream	N/A	N/A	• Superficial fungal infections	
Zinc undecenoate, terpineol, and undecenoic acid	Zinc undecenoate 10 g, terpineol 1 ml, undecenoic acid 2 g/25 g. Apply twice daily. If used in conjunction with ointment or powder apply only once a day	Ointment Powder	N/A	N/A	• Fungal skin infections • Auxiliary treatment vulvae • Flexural infectious eczema • Psoriasis and neurodermatitis	

References:

1. Emims electronic database. Prothiaden. Assessed 5 April 2014.
2. Snyman JR, editor. MIMS Desk Reference. Volume 46 2011 ed. Johannesburg: Times Media; 2011.
3. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
4. Fungizone® (amphotericin-B) - Bristol-Myers Squibb package insert. Available from: http://www.bmscanada.ca/static/products/en/pm_pdf/Fungizone_EN_PM.pdf
5. Epocrates Online. Epocrates. Online database Assessed 5 April 2014
6. Essential Medicines and Health Products Information Portal. Available from http://apps.who.int/medicinedocs/en/d/Jh2918e/23.2.html
7. eMC. Actavis. Online database Assessed 5 April 14.
8. Kezutyte T, Drevinskas T, Maruska A, Rimdeika R, Briedis V. Study of tolnaftate release from fatty acids containing ointments and penetration into human skin ex vivo. *Acta Pol Pharm.* 2011;68(6):965-973
9. Drugs.com Available from: http://www.drugs.com/news/fda-mandates-black-box-warning-some-antibiotics-12915.html
10. Jacoby & Meyers *Dangerous Drugs.* Available from: http://blackbox.dangerousdrugs.com/black-box-warning-chloramphenicol
11. DrugBank. TMIC. Online database Assessed 5 April 2014
12. Patzsche K, Ritter W, Siefert HM, Weber H, Wegner LA. Pharmacokinetic studies following systemic and topical administration of [14C] bifonazole in man. Arzneimittel-Forschung. 1983;33(5):745-750

Atypical antipsychotics

Mechanism[2,3] of action: The therapeutic effects of antipsychotics appear to be mediated, at least in part by interference with dopamine transmission, particularly via D2 receptors, in the brain. Atypical antipsychotics are generally relatively weak inhibitors of D2 receptors, but have a high affinity for a number of other receptors, including D1, D4, and serotonin2 (5-HT2) receptors. Atypicals mostly share the profile of greater 5-HT2 than D2 antagonism.[2]

Major/"Black box"-type warnings:

Patients with dementia-related behavioural disorders treated with atypical antipsychotics are at an increased risk of death compared to placebo.[3]
Neonates exposed to antipsychotic medication during the third trimester of pregnancy are at risk for extrapyramidal signs and/or withdrawal symptoms following delivery.[5]

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Drug-specific warnings[3]
Amisulpride	Adults: Acute Schizophrenia: 400-800 mg in 2 divided doses (increased if necessary to 1200 mg daily). Administer doses of up to 400 mg as once daily dose, whilst higher doses should be administered twice daily. For mainly negative symptoms, daily doses 50-100 mg are recommended.	Tablets	12 hours	Metabolism is limited, with most of a dose appearing in the urine as unchanged drug	• Schizophrenia	Hepatic enzymatic metabolism to inactive metabolite. Beware of drug interactions involving hepatic enzyme inducers or inhibitors	
Aripiprazole	**Oral:** Adults: Schizophrenia: 10-15 mg once daily (may be increased to a maximum of 30 mg once daily). Bipolar mania: Recommended starting dose is 15 mg once daily with maximum daily dose of 30 mg. **IM Injection:** Adults: Initial dose: 9,75 mg as single IM injection. Effective dosage range is 5,25-15 mg as single injection. A 2nd injection may be administered 2 hours after 1st based on individual clinical status. Maximum daily dose: 30 mg (includes all formulations).	Tablets, IM Injection	75 hours	Faeces (55 %), urine (25 %); primarily as metabolites	• Schizophrenia • Acute mania associated with bipolar disorder	Hepatic enzymatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors	
Clozapine	Treatment-resistant schizophrenia: Adults: 12,5 mg 1-2 times on day 1, followed by 25 mg 1-2 times on day 2; Thereafter increase daily dosage gradually in steps of 25-50 mg up to a 300 mg daily dose (within 14 to 21 days). Maximum: 600-900 mg/day. Elderly: 12,5 mg on first day. May be increased in increments of not more than 25 mg/day. Psychotic disorders in Parkinson's disease: Initial dose not to exceed 12,5 mg in evening. Increase in 12,5 mg increments with maximum 2 increments per week up to maximum 50 mg which should not be reached till end of 2nd week.	Tablets	12 hours	Urine (~50 %) and faeces (30 %) as metabolites and trace amounts of unchanged drug.	• Schizophrenia • Psychotic disorders in Parkinson's disease where standard treatment failed	Hepatic enzymatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors	Significant risk of agranulocytosis, potentially life-threatening. Fatalities due to myocarditis have been reported; highest risk in the first month of therapy, however, later cases also reported. Seizures have been associated with clozapine use in a dose-dependent manner. May also cause orthostatic hypotension (with or without syncope).

Atypical antipsychotics (continued)

Generic name	Usual dosage range[1,2,6]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Drug-specific warnings[3]
Olanzapine	**Oral:** Adults: Psychotic disorders: Initially 5-10 mg/day with target of 10 mg/day. Dosage range: 5-20 mg once daily. Acute mania in bipolar disorder: 10 mg once daily. Dosage adjustment within range of 5-20 mg/day at interval of not less than 24 hours. Prevention of recurrence in bipolar disorder: Initially 10 mg/day. Increase at interval of not less than 24 hrs. Safety of doses > 20 mg/day not established. **Injection:** Adults: IM use only. 10 mg as single IM injection. May be repeated 2 hours after 1st dose and again 4 hours after 2nd dose if necessary. Daily dose not to exceed 30 mg.	Rapitabs, Tablets, Velotabs, IM Injection	30 to 38 hours	Urine (57 %) mainly as metabolites and in faeces (30 %)	• Psychotic disorders including schizophrenia, bipolar disorder, acute agitation	Hepatic enzymatic metabolism as well as non-enzymatic phase II metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors.	Diabetogenic increase in Body Mass Index
Paliperidone	**Oral:** Adults: 6 mg once daily, as a prolonged-release preparation; doses may range from 3-12 mg daily. **IM:** Administer as single injection. Initial: 150 mg on day 1 and 100 mg 1 week thereafter in deltoid muscle. Maintenance: 75 mg monthly with recommended range of 25-150 mg based on individual tolerance and efficacy. To avoid missed monthly doses, injections may be given up to 7 days before/after monthly time point.	Prolonged-release tablets Prolonged release suspension for IM Injection	23 hours (oral)[4] 24-49 days (IM)[6]	59 % excreted unchanged in urine, 32 % excreted as metabolites. Phase 2 metabolism accounts for no more than 10 %.[4]	• Schizophrenia • Prevention of recurrence of schizophrenic symptoms (IM)	Hepatic enzymatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors	With injection, full effect may not be evident for several months
Quetiapine	Adults: Administer twice daily. Schizophrenia: Total daily dose for 1st 4 days: Day 1: 50 mg, day 2: 100 mg, day 3: 200 mg and day 4: 300 mg. Titrate dose from 4th day to effective range of 300-450 mg/day (some require adjustment within 150-750 mg/day range). Bipolar-associated manic episodes: Total daily dose for 1st 4 days: Day 1: 100 mg, day 2: 200 mg, day 3: 300 mg and day 4: 400 mg. Further dosage adjustment up to 800 mg/day by day 6 in increments of no greater than 200 mg/day. Adjust dose within range of 200-800 mg/day. Usual effective dose: 400-800 mg/day.	Tablets, Extended-release tablets	6-7 hours	Urine (73 %), faeces (20 %) as inactive metabolites	• Schizophrenia, acute manic episodes associated with bipolar disorder	Hepatic enzymatic metabolism as well as non-enzymatic phase II metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors	Extrapyramidal symptoms are dose dependent

Atypical antipsychotics (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Drug-specific warnings[3]
Risperidone	**Oral:** Adults: **Schizophrenia:** Administer 1-2 times daily. Initially 2 mg/day increased to 4 mg on 2nd day. Usual optimal dose is 4-8 mg/day. Maximal total daily dose: 16 mg/day. **Behavioural disturbances in patients with dementia:** Initially 0,25 mg twice daily. Individualise in increments of 0,25 mg twice daily not more frequently than every other day. Optimal dose: 0,5-1 mg twice daily. **Conduct and disruptive behavioural disorders in children 5-12 years < 50 kg:** Initially 0,01 mg/kg once daily. Adjust in increments of 0,01 mg/kg once daily every other day. Recommended maintenance dose: 0,02-0,04 mg/kg once daily. **Bipolar mania:** Adults: Once daily dosing. Initial dose: 2-3 mg. Dose adjustments in 1 mg/day increments at intervals of not less than 24 hours. Efficacy range: 1-6 mg/day. **Prolonged release IM:** Establish tolerability with oral risperidone before IM therapy. Adults (including elderly): **Recommended dose:** 25 mg deep IM every 2 weeks. Some benefit from higher doses of 37,5 mg or 50 mg. Upward dose adjustment not more frequently than every 4 weeks. Dose > 50 mg every 2 weeks not recommended.	Tablets, Oral solution, Quicklet tablets Prolonged release suspension for IM injection	**Oral:** 20 hours; **Injection:** 3-6 days	Urine (70 %); faeces (15 %)	• Schizophrenia • Behavioural disturbances in patients with dementia • Conduct and disruptive behavioural disorders in children 5-12 years • Mania in bipolar disorder	Hepatic enzymatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors	Extrapyramidal symptoms are dose dependent
Ziprasidone	**Oral:** Adults: Recommended dose: 40 mg twice daily; Maximum 80 mg twice daily. **IM Injection:** Adults: Recommended dose: 10-20 mg as required to maximum 40 mg/day. 10 mg dose may be repeated every 2 hours. Initial dose of 20 mg may be required which may be followed by further 10 mg dose after 4 hours, thereafter 10 mg dose every 2 hours to maximum 40 mg/day.	Capsules, IM Injection	**Oral:** 7 hours; **IM:** 2-5 hours	Mainly as metabolites in the faeces (66 %) and urine (20 %); < 5 % of a dose appears as unchanged drug	• Schizophrenia	Extensively metabolised by aldehyde oxidase (about 66 % of a dose) and by the cytochrome P450 isoenzyme CYP3A4.	Patients with dementia-related behavioral disorders treated with atypical antipsychotics are at an increased risk of death compared to placebo.

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). October 2012 ed. Johannesburg: Times Media; 2012.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Leikin JB, Paloucek FP, editors. Poisoning and Toxicology Handbook 4th ed. New York: Informa Healthcare; 2008.
4. Brunton L, editor. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed: McGraw-Hill; 2011.
5. Food and Drug Administration. FDA Drug Safety Communications. http://fda.gov/Drugs/DrugSafety/ucm243903.htm. February 2011.
6 Owen RT. Paliperidone palmitate injection: Its efficacy, safety and tolerability in schizophrenia. *Drugs Today.* 2010; 46(7): 464-71.

Benzodiazepines

Mechanism of action: Benzodiazepines facilitate the action of gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the central nervous system. At therapeutic concentrations, benzodiazepines act at $GABA_A$ receptors and increase the frequency of openings at GABA-activated chloride-channels which allows for membrane hyperpolarisation and putative downstream reduction in conductive impulse.[2-5]

Major/"Black box"-type warnings: Tolerance in treatment with benzodiazepines can develop rapidly and 15-44 % of chronic users experience withdrawal symptoms when their benzodiazepine dose is decreased. Patients taking benzodiazepines for longer than 3 months are at risk of developing withdrawal.[2,3]
Withdrawal seizures (single, multiple or status epilepticus) have been reported in association with discontinuation.[7]
Floppy infant syndrome of the newborn if given to mothers during pregnancy or labour.[1]
Do not use as single treatment in depression or anxiety with depression as suicide may be precipitated in such patients.[1]
Paradoxical stimulation may occur at extremes of age and in patients with impaired brain function (de-repression)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life* (h)[2-4]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]
Alprazolam	Anxiety: Initially 0,25-0,5 mg 3 times daily. Dosage range: 0,5-4 mg daily in divided doses. Mixed anxiety/depression, anxiety associated with depression: Initially 0,5 mg 3 times daily. Dosage range: 1,5-4,5 mg daily in divided doses. Panic disorders: 0,5-1,0 mg at bedtime or 0,5 mg 3 times daily, adjusted to patient response. Geriatric patients: 0,25 mg 2-3 times daily.	Tablets Slow-release tablets	11-15 hours	Urine (as unchanged drug and metabolites)	• Anxiety • Anxiety associated with depression • Panic-related disorders	Hepatic enzymatic metabolism to active metabolite. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Bromazepam	Adults: Dosage range: 1,5-3 mg 3 times daily. Severe cases: 6-12 mg 2-3 times daily.	Tablets	17 hours	Urine (69 %), as metabolites	• Anxiety	Hepatic enzymatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Brotizolam	Adults: 0,25 mg at night. Elderly: 0,125 mg at night. Treatment duration should be as short as possible with 2 week maximum.	Tablets	5 hours	Kidney 65 % Faeces 21 %	• Sedation	Hepatic enzymatic metabolism to active metabolite. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Chlordiazepoxide	Adults: 20-40 mg daily. Children: 5-10 mg daily (increased to 20 mg daily if necessary). Mild stress disturbances: 5-10 mg daily. Severe cases: 50-100 mg daily. Hospitalised patients: Dose may be increased to 100 mg daily. Recommended dose: 25 mg daily in evening or at bedtime	Tablets	10 ± 3,4 hours	Urine mainly as conjugated metabolites	• Anxiety • Tension muscle spasm	Hepatic enzymatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Clobazam	Adults: 10-30 mg daily in divided doses or at night. Doses exceeding 20 mg should preferably be administered at bedtime or in divided doses.	Capsules, Tablets	18 hours	Urine (90 %), unchanged and as metabolites	• Anxiety • Pre-op medication • Alcohol withdrawal	Hepatic enzymatic metabolism to active metabolite followed by non-enzymatic hepatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Clonazepam	**Injection:** Status epilepticus: Infants and children: 0,5 mg by slow IVI/IV infusion. Adults: 1 amp by slow IVI (not to exceed 0,25-0,5 mg/min). Repeat as required to maximum 10 mg/day in adults. **Oral:** Initial daily dose in infants and children up to 10 years/30 kg body mass: Initially: 0,01-0,03 mg/kg body mass/day in 2-3 divided dosages increased by no more than 0,25-0,5 mg every 3rd day to maintenance dose of 0,1-0,2 mg/kg body mass/day. Do not exceed 0,2 mg/kg body mass/day. Children 10-16 years: Initially 1-1,5 mg/day in 2-3 divided dosages increased by 0,25-0,5 mg every 3rd day to individual maintenance dose of 3-6 mg/day. Adults: Maximum initial dose of 1,5 mg/day in 3 divided doses. Increase by 0,5 mg every 3rd day until adequate control achieved. Usual maintenance dose is 3-6 mg/day. Maximum: 20 mg daily.	Oral drops, Injection, Tablets	23 ± 5 hours	Urine; metabolites excreted as glucuronide or sulfate conjugates	• Epilepsy	Non-enzymatic hepatic metabolism

Benzodiazepines (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life* (h)[2-4]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]
Dipotassium clorazepate	Adults: 15 mg at bedtime. Treatment duration not to exceed 8-12 weeks including tapering-off period.	Capsules	48-96 hours (desmethyldiazepam); 6-8 hours (oxazepam)	Urine	• Anxiety	Decarboxylated rapidly at the low pH in the stomach to form desmethyldiazepam; hepatically to oxazepam
Diazepam	**Injection:** Severe anxiety/acute muscle spasms: 10 mg IM/IV (may be repeated after 4 hours if needed). Tetanus: 100-300 µg/kg body mass IV (may be repeated 1-4 hourly). Status epilepticus: Adults: 150-250 µg/kg IM/IV (may be repeated after 30-60 minutes). Minor surgical procedures: 100-200 µg/kg adjusted to patient's requirements. Sedation in children: Up to 200 µg/kg body mass. Status epilepticus/severe recurrent seizures in children: 200-300 µg/kg body mass OR 1 mg/year of age (may be repeated after 30-60 minutes). Elderly/debilitated: Not more than half the usual adult dose. **Oral:** Mild disorders: Adults: 2 mg 3 times daily. Severe cases: 15-30 mg/day in divided doses (main dose in evening). Hypnotic: 5-10 mg at night. Muscle spasms: 2-15 mg/day in divided doses, increased in severe spastic disorders (e.g. cerebral palsy) to max 60 mg daily.	Injection, Tablets	20-50 hours	Urine, mainly in the form of free or conjugated metabolite	• Sedation • Anxiety • Epilepsy • Muscle spasm • Alcohol withdrawal	Hepatic enzymatic metabolism. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Flunitrazepam	Adults: 0,5-1 mg daily, administered immediately before retiring. Duration not to exceed 4 weeks including tapering off. Elderly: 0,5 mg/day.	Tablets	16-35 hours	Urine as metabolites	• Sedation	Hepatic enzymatic metabolism to active metabolites. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Flurazepam	Adults: Usually 15-30 mg daily within 1 hour of retiring (dosage range: 15-60 mg). Elderly and debilitated patients: Initially 15 mg adapted as necessary. Duration not to exceed 4 weeks including tapering off.	Capsules	74 ± 24 hours	Urine, mainly as conjugated metabolites	• Sedation	Hepatic to N-desalkylflurazepam; also via the small bowel mucosa
Loprazolam	Adults: 1-2 mg at bedtime. Elderly and debilitated patients: Initially 0,5-1,0 mg. Duration not to exceed 4 weeks including tapering-off period.	Tablets	7-8 hours	Urine (minimal as unchanged drug)	• Sedation	Hepatic[6]
Lorazepam	**Oral:** Adults: 2-3 mg/day in divided doses. Elderly/debilitated: 1-2 mg daily in divided doses. **Sublingual:** Premed: Night before procedure: 2 mg. Pre-procedure: 2 mg 1-2 hours before procedure. If heightened sedative effect desired: 0,05 mg/kg to maximum 4 mg. Acute anxiety states: 2-4 mg. **Injection:** Premed: IV administration: 0,044 mg/kg 15-20 minutes pre-op. IM administration: 0,05 mg/kg 2 hrs pre-op. Acute anxiety: Initially: 2-4 mg IM/IV (IV preferred) (i.e. 0,05 mg/kg), which may be repeated in 2 hours if necessary. Status epilepticus: 18 years and older: Initially 4 mg by slow IVI (2 mg/min). Additional 4 mg IV may be administered after 10-14 min observation if needed. Max 8 mg/12 hours.	Injection, Sublingual tablets, Tablets	10-20 hours	Urine; Faeces (minimal)	• Anxiety • Pre-medication • Epilepsy	Non-enzymatic hepatic metabolism

Benzodiazepines (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life* (h)[2-4]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]
Lormetazepam	Adults: 1-2 mg at night. Elderly: 0,5-1 mg half an hour before retiring. Pre-med: 2 mg on night before surgery.	Capsules	11 hours	Urine	• Sedation	Non-enzymatic hepatic metabolism
Midazolam	**Oral:** Insomnia: Adults: Dosage range: 7,5-15 mg immediately before retiring. Pre-med: 15 mg 30 minutes to 1 hour pre-op. Treatment duration not to exceed 2 weeks. **Injection:** Consult product literature for complete dosage guidelines.	Injection, Tablets	2 hours	Urine and faeces (< 10 %), mainly as glucuronide conjugates	• Sedation • Pre-medication • Anaesthetic induction and maintenance	Hepatic enzymatic metabolism to active metabolites. Beware of drug interactions involving hepatic enzyme inducers or inhibitors
Nitrazepam	Adults: 5-10 mg at bedtime. Children: 0,4-1 mg/kg body mass (2,5-5 mg). Elderly pts: 2,5-5 mg. Duration not to exceed 4 weeks including tapering-off period.	Tablets	24-30 hours	Renal (80 %); Faeces (20 %) as metabolites	• Sedation	Hepatic, mainly by nitroreduction followed by acetylation
Oxazepam	Adults: Mild to moderate anxiety: 10-15 mg 3-4 times daily. Severe anxiety, agitation: 15-30 mg 3-4 times daily.	Tablets	2,8-5,7 hours	Urine (as unchanged drug 50 % and metabolites)	• Anxiety • Tension • Alcohol withdrawal	Non-enzymatic hepatic metabolism
Prazepam	Adults: Usually 30 mg/day. Dosage range: 20-60 mg daily. Elderly/debilitated: Initially 10-15 mg daily. Single daily bedtime dose ranges between 20-40 mg. Duration of treatment should not exceed 6-8 weeks including tapering-off period.	Tablets	30-100 hours (metabolite)	Renal and faeces (71 %)	• Anxiety	Hepatic
Temazepam	Adults: 10-30 mg 30 minutes before retiring. Pre-med: 20-30 mg 30 minutes to 1 hour before procedure.	Capsules	8-15 hours	Urine as inactive metabolites	• Sedation • Pre-medication	Hepatic
Triazolam	Adults: 0,25 mg before retiring. Maximum: 0,5 mg. Geriatrics/debilitated patients: 0,125 mg. Duration of treatment not to exceed 4 weeks including tapering-off period.	Tablets	1,5-5,5 hours	Urine, mainly in the form of its conjugated metabolites	• Sedation	Hepatic enzymatic metabolism to active metabolites. Beware of drug interactions involving hepatic enzyme inducers or inhibitors

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). October 2012 ed. Johannesburg: Times Media; 2012.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Leikin JB, Paloucek FP, editors. Poisoning and Toxicology Handbook 4th ed. New York: Informa Healthcare; 2008.
4. Brunton LL, Blumenthal DK, Buxton IL, Parker KL. Goodman and Gilman's Manual of Pharmacology and Therapeutics. New York: McGraw-Hill Professional; 2007.
5. Rossiter D, editor. South African Medicines Formulary. Cape Town, South Africa: Health and Medical Publishing Group of the South African Medical Association; 2010.
6. Humpel M, Stoppelli I, Milia S, Rainer E. Pharmacokinetics and biotransformation of the new benzodiazepine, lormetazepam, in man. III. Repeated administration and transfer to neonates via breast milk. *European Journal of Clinical Pharmacology.* 1982;21(5):421-5. PubMed PMID: 6122580.
7. XANAX® http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018276s045lbl.pdf

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Major/"Black box"-type warnings: NSAIDS lead to an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. The risk may increase with the duration of use. NSAIDs may cause an increased risk of serious gastro-intestinal adverse events, including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastro-intestinal events.[3,7,8]

Non-selective COX inhibitors

Mechanism of action:[2,4,7] Inhibit prostaglandin synthesis non-selectively by decreasing the activity of the enzymes, cyclo-oxygenase-1 and 2, which results in decreased formation of prostaglandin precursors. These effects are directly related to their mechanism of action. Like other NSAIDs, aspirin and other salicylates are inhibitors of the COX-enzyme. However, aspirin (though not the non-acetylated salicylates) irreversibly acetylates the enzyme whereas other NSAIDs compete with arachidonic acid for the active site. This means that aspirin inactivates the enzyme for the life-span of the enzyme and is recovery-dependent on new production; platelets are therefore inhibited for the lifespan of the platelet.

Metabolism:[2,3,9] NSAIDs are metabolised in the liver largely by the hepatic enzyme families CYP 3A4 or CYP2C (phase I) followed by phase II mechanisms (glucuronidation to produce a water-soluble, excretable product), whereas some and others by direct glucuronidation alone. Beware of drug interactions involving hepatic enzyme inducers or inhibitors.

Non-selective COX inhibitors: Acetic acids

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings[7,8,9]
Diclofenac	**Oral:** Adults: 25-50 mg 3 times daily. Maximum daily dose: 150 mg. Children: 0,5-2 mg/kg body mass in 2-3 divided doses. **Injection:** Adults: 75 mg deep intragluteal IM once daily (may be increased to twice daily in severe cases). Total maximum daily dose is 150 mg. **Rectal:** Adults: 100 mg per day. Children: 2-3 mg/kg body mass daily in 2-3 divided doses.	Gel, Tablets, Injection, Powder for oral solution, Suppositories, Dispersible tablets, Slow-release tablets, Capsules, Eye drops	< 2 hours	Excreted in urine (65 %) and bile (35 %) in the form of glucuronide and sulfate conjugates; less than 1 % is excreted as unchanged diclofenac	• Pain • Inflammation	Contra-indicated for the treatment of pain in the setting of coronary artery bypass graft surgery
Indomethacin	**Oral:** Adults: 25 mg two or three times daily (increased, if required, by 25 to 50 mg at weekly intervals to 150 to 200 mg daily) with food. **Topical solution:** 2 ml on affected area 3-5 times daily. Maximum 25 ml (~200 mg) per day. **Rectal:** 100 mg on retiring.	Gel, Capsules, Suppositories, Solution	4,5 hours (inhibition of COX enzyme is irreversible and result in longer duration of effect)	Urine (60 %, primarily as glucuronide conjugates); faeces (33 %, primarily as metabolites)	• Pain, • Inflammation	Irreversible inhibiton of COX increases side effects
Ketorolac	**Oral:** 10 mg 4-6 hourly as required (maximum 40 mg/day). **Ophthalmic:** 1 drop 4 times daily for up to 4 days. **Injection:** Refer to product literature.	Ophthalmic solution, Injection, Tablets	4-6 hours	Urine (~90 %) and faeces as unchanged drug and conjugated and hydroxylated metabolites	• Pain	Contra-indicated in nursing mothers due to potential adverse effects in neonates

Non-selective COX inhibitors: Propionic acids

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings[7,8,9]
Flurbiprofen	**Topical:** One 40 mg patch twice daily; **Oral lozenge:** 8,75 mg (1 lozenge) 3-6 hourly (Maximum 5 lozenges/24 hours)	Patches, Lozenges	3-6 hours	Urine (primarily as metabolites)	Local • Pain • Inflammation	
Ibuprofen	**Oral:** Adults: 200-400 mg 4-6 hourly (maximun 2 400 mg/day). Children: Do not administer to children < 7 kg or under 1 year. Juvenile rheumatoid arthritis: 20 mg/kg daily in divided doses up to 40 mg/kg/day. Pain: 5 mg/kg body mass with a 2nd dose after 2 hours if needed, thereafter 4-6 hourly. Fever: 5 mg/kg body mass 6 hourly. **Injection:** Administer only by IV infusion over 15 minutes, preferably undiluted. Course of 3 doses at 24 hour interval, adjusted according to body mass. 1st injection: 10 mg/kg. 2nd and 3rd injection: 5 mg/kg.	Tablets, Capsules, Film-coated tablets, Oral suspension, Caplets, Slow-release capsules, Injection	2-4 hours	Urine (1 % as free drug) and faeces (minor) mainly as metabolites and their conjugates	• Pain, • Inflammation, • Fever	
Ketoprofen	**Oral:** Adults: 200 mg daily with food. **Topical:** Adults: Apply 5-15 cm gel to affected area 1-2 times daily for up to 7 days.	Gel, Capsules	2-4 hours	Urine (~80 %, primarily as glucuronide conjugates)	• Pain, • Inflammation	

Nonsteroidal anti-inflammatory drugs (NSAIDs) (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings[7,8,9]
Naproxen	**Oral:** Adults: Rheumatoid arthritis, osteo-arthrosis, ankylosing spondylitis: 500 mg-1 g/day in 2 divided doses at 12 hour intervals. Gout: 750 mg immediately, then 250 mg 8 hourly. Acute musculoskeletal disorders: 250 mg 2-3 times daily for 7-14 days. Dysmenorrhoea: 500 mg initially, then 250 mg 6-8 hourly. Rectal: Adults: 1 suppository (500 mg) at bedtime administered in conjunction with oral therapy. Total oral and rectal dose not to exceed 1 g/day.	Tablets, Caplets, Enteric-coated tablets, Suppositories	12-17 hours	Urine (95 %), faeces (< 5 %) as naproxen and -O-desmethylnaproxen and their conjugates	• Pain, • Inflammation, • Fever	
Naproxen Esomeprazole	Adults: 500 mg naproxen and 20 mg esomeprazole twice daily	Tablets	Esomeprazole: 1 hour Naproxen: 15 hours	Metabolites excreted Esomeprazole: ~80% urine ~20 % faeces Naproxen Urine (95 %), faeces (< 5 %) as naproxen and -O-desmethylnaproxen and their conjugates	• Osteoarthritis, • Rheumatoid arthritis • Ankylosing spondylitis • Decrease risk of developing NSAIDs-associated gastric ulcers Not recommended for initial treatment of acute pain	Contra-indicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft. Naproxen may cause an increased risk of cardiovascular thrombotic events, myocardial infarction and stroke. Naproxen causes an increased risk of serious gastro-intestinal adverse events
Non-selective COX inhibitors: Enolic acid						
Generic name	**Usual dosage range[1,2]**	**Dosage forms[1]**	**Half life[2,3]**	**Elimination[2,3]**	**Therapeutic area[1,2]**	**Drug-specific warnings[7,8,9]**
Lornoxicam	**Injection:** Adults: Administer IV/IM. Administer in 8 mg doses (daily dose not to exceed 16 mg). A further 8 mg within 1st 24 hours may be needed. **Oral:** Adults: Pain: 8-16 mg/day in 2-3 divided doses. Maximum total daily dose is 16 mg.	Injection, Tablets	3 to 5 hours	Urine and faeces[2,3,5,6]	• Pain	
Piroxicam	**Topical:** Apply 3 cm 3-4 times daily to affected area. **Oral:** Adults: Ankylosing spondylitis, rheumatoid and osteoarthritis: 20 mg daily, although doses of 10-30 mg daily have been used. Acute musculoskeletal disorders: 7-14 days treatment. Initially 40 mg daily for 2 days, then 20 mg daily. Acute gout: 40 mg daily for 5-7 days.	Tablets, Capsules, Dispersible tablets, Gel	45-50 hours	Primarily urine and faeces (small amounts) as unchanged drug (5 %) and metabolites	• Pain, • Inflammation	
Non-selective COX inhibitors: Anthranillic acid						
Generic name	**Usual dosage range[1,2]**	**Dosage forms[1]**	**Half life[2,3]**	**Elimination[2,3]**	**Therapeutic area[1,2]**	**Drug-specific warnings[7,8,9]**
Mefenamic Acid	**Oral:** Adults: Mild to moderate pain: 500 mg 3 times daily. Acute pain: Initially 500 mg thereafter 250 mg 6 hourly. Children: 25 mg/kg/body mass daily in divided doses. Repeat up to 3xdly. 6 months-1 year: 5 ml. 2-4 years: 10 ml. 5-8 years: 15 ml. 9-12 years: 20 ml. **Rectal:** Children 6 months-2 years weighing not less than 10 kg: 1 suppository 3 times per day at 6-8 hour intervals. Use longer than 24 hours not recommended.	Capsules, Tablets, Paediatric suspension, Suppositories	2-4 hours	Urine (< 50 %) and faeces as unchanged drug and, mainly, as conjugates of mefenamic acid and its metabolites	• Pain, • Inflammation, • Fever	

Nonsteroidal anti-inflammatory drugs (NSAIDs) (continued)

Non-selective COX inhibitors: Aspirin and other salicylates

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings[7,8]
Aspirin	Usual analgesic and antipyretic dose: 300 to 900 mg, repeated every 4 to 6 hours according to clinical needs (up to maximum 4 g daily). Cardiac/ischaemic indications: 100-300 mg daily, preferably at the same time daily.	Tablets, Effervescent tablets	~1-3 hours	Urine (as metabolites and unchanged active)	• Pain, • Fever • Prophylaxis of arterial clotting in preventing coronary artery occlusion	Use caution in patients with known G6PD deficiency and in patients with asthma.

Selective COX inhibitors

Mechanism of action:[2,4,7] Inhibit prostaglandin synthesis by selectively inhibiting the activity of the enzyme, cyclo-oxygenase-2 (COX-2), which results in decreased formation of prostaglandin precursors. This is also called COX-1 sparing which accounts for this class's better GIT tolerability

Metabolism:[2,3] NSAIDs are metabolised in the liver largely by the hepatic enzyme families CYP 3A4 or CYP2C (phase I) followed by phase II mechanisms (glucuronidation to produce a water-soluble, excretable product), whereas some and others by direct glucuronidation alone.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Drug-specific warnings[7,8]
Celecoxib	Adults: Osteoarthritis: 200-400 mg as single dose or 2 divided doses. Rheumatoid arthritis: 100-200 mg twice daily day. Pain post dental surgery: 100-200 mg up to maximum daily dose of 400 mg. Mild to moderate post-op pain: 200-400 mg daily. Mild to moderate musculoskeletal pain: Recommended dose: 200 mg twice daily. Mild to moderate primary dysmenorrhagic pain: 400 mg initially followed by additional 200 mg dose if needed on 1st day, thereafter 200 mg twice daily on subsequent days. Ankylosing spondylitis: 200 mg daily as single dose or 100 mg twice daily. Some patients benefit from total daily dose of 400 mg.	Capsules	11 hours	Urine (27 %), Faeces (57 %) as metabolites	• Pain, • Inflammation	Consider alternative therapy. Use smallest effective dose for shortest time necessary due to dose-dependent increase in risk of CV events. Only use in patients who have not achieved pain control with non-selective NSAIDs
Etoricoxib	Adults: Osteoarthritis: 60 mg once daily. Rheumatoid arthritis: 90 mg once daily. Acute gouty arthritis: 120 mg once daily only during acute symptomatic period and limited to 8 days.	Tablets	22 hours	Urine (70 %), Faeces (20 %)	• Pain, • Inflammation	Consider alternative therapy. Use smallest effective dose for shortest time necessary due to dose dependent increase in risk of CV events. Only use in patients who have not achieved pain control with non-selective NSAIDs
Meloxicam	**Oral:** Adults: Rheumatoid arthritis, ankylosing spondylitis: 15 mg/day reduced to 7,5 mg/day according to response. Osteoarthritis, acute sciatica: 7,5 mg/day which may be increased to 15 mg/day. Maximum dose: 15 mg/day. **Injection:** Adults: Administer deep IM for maximum 3 days, thereafter continue with oral preparation. Rheumatoid arthritis, ankylosing spondylitis and osteoarthritis: 7,5 mg-15 mg once daily. Acute sciatica: 7,5 mg/day increased if necessary to 15 mg/day if no improvement.	Tablets, Injection	20 hours	Urine and faeces (as inactive metabolites)	• Pain, • Inflammation	Consider alternative therapy. Use smallest effective dose for shortest time necessary due to dose dependent increase in risk of CV events. Only use in patients who have not achieved pain control with non-selective NSAIDs
Parecoxib	Adults: Recommended dose: Initially 40 mg IV/IM, followed by 20 mg or 40 mg 6-12 hourly. Maximum daily dose of 80 mg.	Powder for injection	8 hours	Urine, mainly as inactive metabolites	• Pain	Consider alternative therapy. Use smallest effective dose for shortest time necessary due to dose dependent increase in risk of CV events. Only use in patients who have not achieved pain control with non-selective NSAIDs

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). October 2012 ed. Johannesburg: Times Media; 2012.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Leikin JB, Paloucek FP, editors. Poisoning and Toxicology Handbook 4th ed. New York: Informa Healthcare; 2008.
4. Finkel R, Clark MA, Cubeddu LX, editors. Lippincott's illustrated reviews: Pharmacology. 4th ed. Baltimore: Lippincott Wiliams & Wilkens; 2010.
5. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam. A short half-life oxicam. *Clinical Pharmacokinetics.* 1998;34(6):421-8.
6. Bonnabry P, Leemann T, Dayer P. Role of human liver microsomal CYP2C9 in the biotransformation of lornoxicam. *European Journal of Clinical Pharmacology.* 1996;49(4):305-8.
7. Antman EM, Bennet JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of Nonsteroidal Anti-inflammatory Drugs. An Update for Clinicians. A Scientific Statement From the American Heart Association. *Circulation.* 2007;115:0000-0000.
8. Beach JE, Faich GA, Bormel FG, Sasinowski FJ. Black Box Warnings in Prescription Drug Labelling: Results of a Survey of 206 Drugs. *Food and Drug Law Journal.* 1998;53:403-411.
9. AVimovo®: Highlights of prescribing information. Available from http://www.vimovo.com/full-prescribing-information.aspx

Lipid-lowering agents

HMG-CoA reductase inhibitors (statins)

Mechanism of action:[2,4] Mevalonic acid-like moiety competitively inhibits HMG-CoA reductase. HMG-CoA is responsible for catalysing cholesterol synthesis, therefore inhibition of HMG-CoA decreases cholesterol synthesis. This then results in a compensatory increase in LDL receptors in hepatic and extra-hepatic tissues, which results in increased removal of LDL from the blood. Statins also enhance removal of LDL precursors (VLDL and IDL) and decrease hepatic VLDL production. This mechanism also likely accounts for TG-lowering effect of statins[4]

Metabolism:[2,3,6,7] Statins undergo high first pass metabolism by the liver, largely by the hepatic enzyme families CYP 3A4 or CYP2C (phase I) followed by phase II mechanisms (glucuronidation to produce a watersoluble, excretable product). Agents such as atorvastatin, simvastatin and to a lesser extent, rosuvastatin are candidates for interaction with enzyme inhibitors.

Major/ "black box"-type warning: Rhabdomyolosis with renal failure; Incidence and severity of myopathy increased by drug interactions[1,3,4]

Generic name	Usual dosage range[1-3]	Dosage form[1,3]	Half life* (hours)[2]	Elimination[2]	Therapeutic area[1,2,3]	Drug-specific warnings
Atorvastatin	10-80 mg once daily[1,3]	Tablets[1]	Parent compound 7-14 hours, longer in elderly - 19 hours[2,3]	Majority excreted via billiary route by liver, less than 2 % recovered from urine[2,3]	• Hypercholesterolaemia[1,3]	
Fluvastatin	20-80 mg daily at night	Capsules[1] XL Tablets[1]	1-3 hours[2,3]	95 % excreted via billiary route into faeces, 5 % in urine[2,3]	• Hypercholesterolaemia[1,3]	
Pravastatin	10-80 mg once daily at night[1,3]	Tablets[1]	Parent compound 2,6-3,2 hours[2]	70 % excreted in faeces and 20 % in urine[2,3]	• Hypercholesterolaemia[1,3] • Reducing CV risk in coronary heart disease[1,3]	
Rosuvastatin	5-40 mg once daily[1,3]	Tablets[1]	19 hours[2,3]	90 % eliminated unchanged in faeces[2,3]	• Hypercholesterolaemia[1,3]	
Simvastatin	5-80 mg once daily in the evening[1,2,3]	Tablets[1]	1,9 hours[2,3]	> 60 % secreted into bile and excreted in faeces; 13 % excreted in urine.[2,3]	• Hypercholesterolaemia[1,3] • Reducing CV risk in coronary heart disease[1,3]	Maintain patients on 80 mg/day dose only if they have been taking this dose for 12 or more months without evidence of muscle toxicity. Do not start new patients on 80 mg/day[8]

Cholesterol absorption inhibitors

Mechanism of action:[2,3] Inhibit the intestinal absorption of cholesterol and related plant sterols

Metabolism:[2] Primarily metabolised in the small intestine and the liver via phase II metabolism

Generic name	Usual dosage range[1-3]	Dosage form[1,3]	Half life* (hours)[2]	Elimination[2]	Therapeutic area[1,2,3]	Drug-specific warnings
Ezetimibe	10 mg/day as a single dose[1,3]	Tablets:[1,3]	Parent compound:[2] 19-30 hours Metabolites:[2] Ezetimibe glucuronide 13-20 hours	78 % excreted in the faeces, 11 % excreted in the urine[2]	• Primary hypercholesterolaemia alone or with a HMG CoA reductase inhibitor.[1,3] • Homozygous familial hypercholesterolaemia in conjunction with a HMG CoA reductase inhibitor[1,3]	Myopathy including rhadomyolysis may occur.[2] Risk is increased with - concomitant use of HMG CoA reductase inhibitor or fibrate[2]

Fibrates

Mechanism of action:[3] Act at several points in lipid and lipoprotein metabolism by regulating gene expression through the peroxisomal proliferator receptor alpha system

Metabolism:[2]

Bezafibrate: Metabolised in liver via hydroxylation and glucuronidation; hydrolytic cleavage by microsomal mixed-function oxidases may also be involved[2]

Fenofibrate: Metabolised in liver and kidneys via glucuronidation[2]

Gemfibrozil: Metabolised in liver via oxidation[2]

Major/"black box"-type warning:[1,2] Rhabdomyolysis with impaired renal function. Drug-induced myopathy

Generic name	Usual dosage range[1-3]	Dosage form[1,3]	Half life* (hours)[2]	Elimination[2]	Therapeutic area[1,2,3]	Drug-specific warnings
Bezafibrate	200 mg daily - 200 mg two to three times daily[1,2,3] Controlled-release: 400 mg daily[1,2,3]	Tablets[1,3] SR tablets[1,3] Retard tablets[1,3]	Parent compound: 2 hours.[2,3,5]	About 94 % is excreted in the urine.[2,3,5]	• Primary hyperlipidaemia of types IIa, IIb, III, IV and V.[1,3,6] • Secondary hyperlipidaemia.[1,3,6]	Blood dyscrasias.[1,2] Erythema multiforme[1,6] Stevens-Johnson syndrome.[1,6] Toxic Epidermal necrolysis.[1,6]
Fenofibrate (micronised)	200 mg daily[1,3]	Capsule[1,3]	Parent compound: 20-22 hours[2,3,4]	About 80 % is excreted in the urine.[3]	• Hyperlipoproteinaemia of types IIa, IIb, III, and IV.[1]	

Lipid-lowering agents (continued)

Generic name	Usual dosage range[1-3]	Dosage form[1,3]	Half life* (hours)[2]	Elimination[2]	Therapeutic area[1,2,3]	Drug-specific warnings
Gemfibrozil	600 mg-1 500 mg daily in 2 divided doses.[1,3]	Tablets[1,3]	Parent compound: 1,5 hours[2]	About 70 % is excreted in the urine.[2,3]	• Treatment of type IIb and type IV hyperlipidaemias[1,3]	Inhibits glucuronidation in the hepatocyte and thus potentiates the toxicity of HMG CoA reductase inhibitors.[3]

Niacin derivates

Mechanism of action:

Acipimox:[2,6] Inhibit the release of fatty acids from adipose tissue and reduce the blood concentration of VLDL and LDL, resulting in a reduction in triglyceride and cholesterol levels

Niacin/laropiprant:[6] Niacin inhibits the release of free fatty acids from adipose tissue, ultimately resulting in reduced levels of LDL, total cholesterol, VLDL, apo B, triglycerides and lipoprotein A and increased levels of HDL and apo A-I. Laropiprant is a selective antagonist of DP1 that inhibits niacin-induced flushing.

Metabolism:[2,3,6] Acipimox is excreted unchanged. Niacin undergoes extensive first-pass metabolism and Laropiprant is primarily metabolised by liver phase II metabolism and to a lesser extent phase I enzymatic metabolism, primarily by CYP3A4

Generic name	Usual dosage range[1-3]	Dosage form[1,3]	Half life* (hours)[2]	Elimination[2]	Therapeutic area[1,2,3]	Drug-specific warnings
Acipimox	500-750 mg/day in divided doses.[1,3]	Capsules:[1,3]	2 hours[2,3]	86 %-90 % excreted in the urine. 4,5 % excreted in the faeces[2]	• Type IIa, IIb, and IV lipid disorders[1]	
Niacin/ laropiprant	1 g/20 mg-2 g/40 mg daily[6]	Tablets:[6] Niacin extended release 1 g plus laropiprant Immediate release 20 mg	Niacin: 20-60 minutes.[7] Laropiprant: 17 hours.[6]	Niacin: 60-75% excreted in urine as metabolites.[6] Laropiprant: 68 % excreted in the faeces as parent compound and 22 % in the urine as metabolites.[2]	• Primary hyper-cholesterolaemia[6] • Mixed dyslipidaemia[6]	Severe hepatic toxicity, including fulminant hepatic necrosis, has occurred in patients who have switched from immediate-release niacin to sustained release niacin products at equivalent doses.[6]

Bile acid sequestrant

Mechanism of action:[2,3] Binds bile salts in the intestine. Results in increased faecal loss of bile acid, increased oxidation of cholesterol to bile acids and a decrease in serum cholesterol and LDL levels

Metabolism: Not metabolised

Generic name	Usual dosage range[1-3]	Dosage form[1,3]	Half life* (hours)[2]	Elimination[2]	Therapeutic area[1,2,3]	Drug-specific warnings
Choles-tyramine	Adult: Primary Hypercholestero-laemia: Initial dose: 4 g once or twice a day. Increasing gradually as required, at intervals of not less than four weeks, to a maximum of 24 g daily given in up to four divided doses[1,3,6] Pruritis associated with partial biliary ob-struction: 4-8 g daily[1,3] Diarrhoea due to bile acid malabsorption: 4 g three times a day, adjusted as needed. Alternative treatment should be sought if no response is seen within three days.[1,3]	Powder[1,2]	Not absorbed[2]	100 % excreted in the faeces.[2]	• Primary hypercholesterolaemia.[1,3,6] • Pruritis associated with partial biliary obstruc-tion.[1,3,6] • Diarrhoea due to bile acid malabsorption.[1,3,6]	Contains phenylalanine use with caution in patients with phenylketonuria[6]

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS) July 2012 ed. Johannesburg: Times Media; 2012
2. Micromedex® Healthcare Series Vol. 154 expires 12/2012
3. SAMF 2012
4. Goodman and Gilman. The Pharmacological Basis of Therapeutics
5. Martindale, The Extra Pharmacopoeia, 29
6. Package Insert
7. AHFS 2012
8. Food and Drug Administration. FDA Drug Safety Communications. http://fda.gov/Drugs?DrugSafety/ucm256581.htm. December 2011.

Opioids

Mechanism of action: Opioids interact stereospecifically with opiate receptors in the CNS and in other anatomic structures, such as the gastro-intestinal tract and the urinary bladder. Opioids cause hyperpolarisation of nerve cells, inhibition of nerve firing and presynaptic inhibition of transmitter release, inhibiting ascending pain pathways, altering the perception of and response to pain.[2-5]

Major/"Black box"-type warnings:[3,10] Opioids can produce physical dependence and withdrawal symptoms if suddenly stopped. They are also subject to abuse and tolerance to pain relief.[3] It should be noted that tolerance to respiratory depression also develops and allows tolerance of higher dosage.
Opioid substances, which include fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone, have the highest potential for abuse and associated risk of fatal overdose due to respiratory depression. Anaphylaxis or anaphylactoid reactions can occur..

Full agonist at mu receptors

Mechanism of action:[2-5] Agonist activity mainly at μ-opioid receptors and possibly at κ and δ receptors

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Major/"Black box"-type warnings[2,3,6-9]
Morphine	**Injection:** Adults: 5-20 mg SC/IM 4 hourly according to patient's morphine needs. Children 6-12 years: 5-10 mg 6 hourly. 1-5 years: 2,5-5 mg 6 hourly. **Oral:** Initially 10-20 mg twice daily adjusted according to pain and tolerance.	Injection Tablets	2 hours	Urine, faeces (10 %) as conjugates	• Pain	Conjugated with glucuronic acid in the liver (phase II) and gut to produce metabolites, most of which are active. Morphine is less metabolised by liver enzymes (phase I) but undergoes entero-hepatic circulation.	Consumption of alcohol while taking morphine may result in the rapid release and absorption of a potentially fatal dose of morphine. Due to the risk of severe and/or sustained cardiopulmonary-depressant effects of injectable form, injectable morphine must be administered in a fully equipped and staffed environment. The pellets in the capsules and tablets are not to be crushed, dissolved, or chewed. Tampering with the formulation, crushing or chewing the pellets or tablets may cause a rapid release and absorption of morphine resulting in a morphine dose which may be fatal, particularly in opioid-naïve individuals.
Codeine	Adults: Pain: 15-60 mg daily	Tablets	2,5-3,5 hours	Metabolites are excreted by the kidney, mainly as conjugates with glucuronic acid.	• Pain	Liver enzyme metabolism to active metabolites.	Nursing infants may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolisers of codeine (codeine is quickly metabolised to morphine). Children receiving codeine may be at risk for developing serious side-effects such as respiratory depression which could lead to death after receiving doses within the recommended ranges due to rapid metabolism to active morphine moyiety.
Dihydro-codeine	**Oral:** Adults: Usually 30 mg every 4-6 hours with or after meals. **Injection:** Adults: Deep SC/IM injection: Up to 50 mg repeated every 4-6 hours if necessary.	Injection, Tablets	3,3-4,4 hours	Excreted in urine as unchanged drug and metabolites	• Pain	Liver enzyme metabolism to active metabolites.	
Alfentanil	Doses are adjusted according to the needs of the patient. Consult product literature for complete dosage guidelines.	Injection	1-2 hours	Urine	• Narcotic analgesic in general anaesthesia • Anaesthetic induction agent.	Liver enzyme metabolism to in-active metabolites.	Metabolism may be reduced by potent inhibitors of liver enzymes resulting in a risk of prolonged or delayed respiratory depression.

Opioids (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Major/"Black box"-type warnings[2,3,6-9]
Fentanyl	Doses are adjusted according to the needs of the patient. Consult product literature for complete dosage guidelines.	Injection, Transdermal patches	2-4 hours; **Transdermal:** 17 hours	Urine (primarily as metabolites, 10 % as unchanged drug)	• Narcotic analgesic supplement in general anaesthesia • In combination with neuroleptic agents as premedication, anaesthetic induction agent and adjunct to anaesthetic maintenance • Anaesthetic agent with O_2 in selected high-risk patients undergoing major surgery • Treatment of post-operative pain • Treatment of intractable chronic pain which cannot be managed by lesser means (transdermal)	Metabolised by liver enzymes	Use in opioid-tolerant patients only. Serious or life-threatening hypoventilation may occur, even in opioid-tolerant patients. Caution is also advised in patients with myasthenia gravis; the effects of muscular rigidity on respiration may be particularly pronounced in these patients. The concomitant use of fentanyl with all cytochrome P450 3A4 liver enzyme inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil), may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression
Remifentanil	Doses are adjusted according to the needs of the patient. Consult product literature for complete dosage guidelines.	Injection	3-10 minutes	Urine (95 % as metabolite)	• Narcotic analgesic or adjunct during induction or maintenance of inhalation anaesthesia during surgical procedures including cardiac surgery • Analgesic and sedative for up to 72 hours in mechanically ventilated intensive care patients	Hydrolysed by non-specific esterases in blood and tissues to an essentially inactive carboxylic acid metabolite.	Remifentanil is not recommended as the sole agent in general anaesthesia, because the loss of consciousness cannot be assured
Sufentanil	Doses are adjusted according to the needs of the patient. Consult product literature for complete dosage guidelines.	Injection	2,5 hours	Urine and faeces as inactive metabolites	**IV Administration:** • Analgesic adjunct in maintenance of general anaesthesia in surgical procedures requiring endotracheal intubation and ventilation. **Epidural:** • Post-operative pain management following general surgery, thoracic or orthopaedic procedures and Caesarean section • Analgesic adjunct to epidural bupivacaine with/ without adrenaline during labour and vaginal delivery.	Metabolised in the liver and small intestine phase I metabolism	Sufentanil can cause severely compromised respiratory depression; use with caution in patients with head injuries, hepatic or renal impairment or with pulmonary disease

Opioids (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Major/"Black box"-type warnings[2,3,6-9]
Methadone	Cough: Adults: 2,5-5 ml 4-6 hourly. Opioid dependence: Initially 20 mg once daily, increased in steps of 10 mg over a 3 week period to 70-80 mg. After stabilisation period of 4 weeks adjust dose to normal dose of 60-120 mg/24 hours. If treatment ineffective or patient cannot tolerate it, discontinue treatment with gradual dosage reduction.	Oral solution, Linctus	15-25 hours	Urine (< 10 % as unchanged drug) Bile as metabolites	• Cough • Opioid dependence	Metabolised by liver enzymes	Deaths, cardiac and respiratory adverse effects, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks

Partial agonist at mu opioid receptors

Mechanism of action:[2-5] Buprenorphine is a partial agonist at μ receptors with some antagonist activity at κ receptors
Pentazocin acts as an agonist on κ receptors and is a weak antagonist at μ and δ receptors

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Major/"Black box"-type warnings[2,3,6-9]
Bupre-norphine	**Transdermal:** Initial use: 5 μg/h patch worn continuously for 7 days. Titrate every 3-7 days until adequate analgesia achieved. **Oral:** Opioid dependence: Induction therapy: Initial dose: 0,8-4 mg as single daily dose (dose may be increased as necessary but maintenance doses should not exceed 16 mg daily). Pain: 0,2-0,4 mg 6-8 hourly as required. **Injection:** 0,3-0,6 mg 6-8 hourly as required	Transdermal patch, Sublingual tablets, Injection	20 to 36 hours	Faeces (mainly as unchanged drug) Urine as metabolites.	• Pain • Substitute treatment for opioid drug dependence	Liver enzyme metabolism (phase I) and phase II to active metabolites followed by phase II metabolism	Opioid analgesics with some antagonist activity, such as buprenorphine, may precipitate withdrawal symptoms in physically dependent patients who have recently used pure agonists such as morphine. Do not exceed a dose of one 20 mcg/hour transdermal buprenorphine due to the risk of QTc interval prolongation. Avoid exposing the transdermal buprenorphine application site and surrounding area to direct external heat sources. Temperature-dependent increases in buprenorphine release from the system may result in overdose and death.
Pentazocine	Adults: 30-60 mg 3-4 hourly IM, IV or SC. IV doses exceeding 30 mg not recommended. Maximum 360 mg daily. Children: 6-12 years: 1 mg/kg body mass IM/SC 3-4 hourly (not exceeding 30 mg). 500 μg/kg body mass IV.	Injection	2-5 hours	Urine as metabolites and small amount of unchanged drug	• Pain	Hepatic	Opioid analgesics with some antagonist activity, such as pentazocine, may precipitate withdrawal symptoms in physically dependent patients who have recently used pure agonists such as morphine.

Other

Mechanism of action:[2-5]
Pethidine interacts predominately with the opioid μ (and possibly δ) receptor(s).
Tramadol is a centrally acting analgesic with selective μ opioid receptor agonist. In addition, it weakly inhibits noradrenaline and serotonin re-uptake.
Hydromorphone interacts predominantly with the opioid mu-receptors, but also binds with kappa-receptors which are thought to mediate spinal analgesia, miosis and sedation.
Oxycodone acts as a weak agonist at mu, kappa, and delta opioid receptors within the central nervous system.

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Major/"Black box"-type warnings[2,3,6-9]
Pethidine	Adults: 50-100 mg SC/IM or reduced dose IV 3-4 hourly. Maximum 150 mg per single dose. Children: 1-1,5 mg/kg body mass IM/SC (not exceeding adult dose)	Injection	3-6 hours	Urine (as metabolites)	• Pain	Liver enzyme metabolism (phase I) and phase II to metabolites followed by phase II metabolism	Use only with extreme caution (if at all) in patients with head injury or increased intracranial pressure (ICP); potential to elevate ICP may be greatly exaggerated in these patients.

Opioids (continued)

Generic name	Usual dosage range[1,2]	Dosage forms[1]	Half life[2,3]	Elimination[2,3]	Therapeutic area[1,2]	Metabolism[2,3]	Major/"Black box"-type warnings[2,3,6-9]
Tramadol	**Oral:** Adults (and children over 14 years): Initially 50 mg followed by 100 mg twice daily. May be increased to 150-200 mg twice daily. Total oral daily dosage should not exceed 400 mg. **Injection:** Adults (and children over 14 years): 100 mg IV/IM/SC (in case of IV administer injection slowly over 2-3 minutes or dilute in solution for infusion). Total daily dose not to exceed 400 mg Post-op pain: Initial bolus of 100 mg. During the 90 minutes following initial bolus further 50 mg doses may be given every 30 minutes up to total dose of 250 mg including bolus. Subsequent doses: 50-100 mg 4-6 hourly up to total daily dose of 600 mg. Less severe pain: 50-100 mg 4-6 hourly.	Capsules, Injection, Tablets, Slow-release tablets, Drops	6-8 hours	Urine (30 % as unchanged drug; 60 % as metabolites)	• Pain	Liver enzyme metabolism	Use with extreme caution in patients receiving MAO inhibitors and/or CNS depressants Relatively contra-indicated in patients using SSRI's
Hydro-morphone	Nature of pain and medical status affect dose selection. Start with lowest appropriate dose and titrate to adequate analgesic level. Do not administer more than once per 24 hours. In patients currently receiving opioids, the initial dose should not exceed 8 mg/24 hours.	Extended release tablets	2,5 hours	Urine (as metabolites)	• Pain	Hepatic via glucuronidation (phase II)	Potential for abuse. For use in opioid-tolerant patients only. Fatal respiratory depression could occur in patients who are not opioid-tolerant.
Oxycodone	Adults over 18 and elderly: Opioid-naive patients with severe pain uncontrolled by weaker opioids: Prolonged-release tablets: Usually 5-10 mg 12 hourly (5 mg 4-6 hourly in case of capsules). Maximum dose mostly 400 mg/day, but few may require higher dose. Patients receiving oral morphine prior to oxycodone therapy: Base daily dose on ratio: 10 mg oral oxycodone = 20 mg oral morphine.	Prolonged release tablets, Capsules	~2-4 hours	Urine (as metabolites and unchanged active)	• Pain	Liver enzyme metabolism (phase I) to active metabolites, followed by phase II metabolism	Potential for abuse. For use in opioid-tolerant patients only. The concomitant use of oxycodone with all cytochrome P450 3A4 inhibitors such as macrolide antibiotics, azole-antifungal agents, and protease inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse effects and may cause potentially fatal respiratory depression. Tablets must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved.

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). October 2012 ed. Johannesburg: Times Media; 2012.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Leikin JB, Paloucek FP, editors. Poisoning and Toxicology Handbook 4th ed. New York: Informa Healthcare; 2008.
4. Finkel R, Clark MA, Cubeddu LX, editors. Lippincott's illustrated reviews: Pharmacology. 4th ed. Baltimore: Lippincott Wiliams & Wilkens; 2010.
5. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician*. 2008;11(2 Suppl):S133-53.
6. Carson S, Thakurta S, Low A, et al. Drug Class Review: Long-Acting Opioid Analgesics: Final Update 6 Report [Internet]. Portland (OR): Oregon Health & Science University; 2011 Jul. Appendix B, Boxed warnings of included drugs. Available from: http://www.ncbi.nlm.nih.gov/books/NBK62343/
7. US Food and Drug Administration. Warning for Nursing Mothers Taking Codeine [updated 29 August 2012; cited 25 February 2013]. Available from: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048740.htm.
8. Avinza [package insert]. Ligand Pharmaceuticals Incorporated, San Diego, CA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021260s006lbl.pdf. Accessed February 25, 2013.
9. US Food and Drug Administration. Post-Surgery Codeine Puts Kids at Risk [updated 20 February 2013; cited 25 February 2013]. Available from: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm315497.htm
10. Durogesic [package insert]. Janssen. Titusville, NJ . http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019813s033lbl.pdf. Accessed February 25, 2013.

Proton pump inhibitors (PPIs)

Major/"black box"-type warnings[6]
PPI therapy may be associated with an increased risk of *C. difficile* diarrhoea. PPI therapy is associated with an increased risk for osteoporosis-related fractures
Avoid concomitant use with methotrexate or clopidogrel
Mechanism of action:[2,5] The PPI prodrug is activated by the parietal cells in an acidic environment, the activated PPI then irreversibly binds to the H^+/K^+ATPase. Binding to the proton pump (H^+/K^+ATPase), prevents the exchange of potassium ions (K^+) for hydrogen (H^+), and therefore acid secretion (basal and meal stimulated).

Generic name[1-5]	Usual dosage range[1,3,4,6]	Dosage forms[1,3,4]	Half life[2]	Elimination[2]	Therapeutic area[1-5]
Esomeprazole	**MUPS tablets:** **Erosive reflux oesophagitis**: 40 mg daily for 4 weeks, continue for 4 weeks if symptoms persists **Relapse prevention of healed oesophagitis:** 20 mg daily **Symptomatic GORD:** No oesophagitis, 20 mg on demand regimen daily, if no symptom control after 4 weeks, investigate further **Continuous NSAID therapy:** 20-40 mg daily ***H. pylori* associated ulcer and prevention of such ulcer:** 20 mg twice daily for 7 days, in combination with 1 g amoxicillin and 500 mg clarithromycin **Granules:** Dissolve sachet content in 15 ml water, leave to thicken and administer within 30 minutes **Erosive reflux oesophagitis:** Adults and children 12 years and older: 40 mg daily for 4 weeks, continue for 4 weeks if symptoms persists. Children 1-11 years: < 20 kg: 10 mg daily for 8 weeks, > 20 kg: 10-20 mg once daily for 8 weeks **Relapse prevention of healed oesophagitis:** Adults and children 12 years and older: 20 mg daily. Children 1-11 years: 10 mg daily **Symptomatic GORD:** Adults and children 12 years and older: No oesophagitis, 20 mg on demand regimen daily, no symptom control after 4 weeks, investigate further. Children 1-11 years: 10 mg daily up to 8 weeks **Continued NSAID therapy:** Adults: 20-40 mg once daily ***H. pylori* associated ulcer and prevention of such ulcer:** Adults: 20 mg twice daily for 7 days, in combination with 1 g amoxicillin and 500 mg clarithromycin **Pathological hypersecretory conditions:** Initially 40 mg twice daily. Individualise up to 120 mg twice daily has been administered **IV:** Administer for shortest possible time, and transfer to oral. Administer injection over 3 minutes infusion 10-30 minutes Dosages: see tablets above **Haemostasis maintenance and prevention of rebleeding of gastric/duodenal ulcer:** 80 mg bolus, followed by 8 mg/hour next 3 days. Follow parenteral therapy with oral administration for 4 weeks.	MUPS Tablets Granules, IV injection and infusion	1,3 hours	Metabolites excreted 80 % urine 20 % faeces	**MUPS Tablets and Granules:** • Erosive oesophagitis, relapse prophylaxis in healed oesophagitis • GORD • Prevention of gastric and duodenal ulcers associated with NSAIDs therapy • Duodenal ulcers and prevention of relapse of such ulcers associated with *H. pylori* infection in combination with appropriate antibiotic • Zollinger Ellison Syndrome (Granules) **IV:** • GORD were oral therapy not appropriate • Erosive reflux oesophagitis • Long-term management of healed oesophagitis to prevent relapse • Short-term haemostasis management and prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers
Lansoprazole	Adults **Gastric ulcer:** 30 mg once daily for up to 8 weeks **Duodenal ulcer:** 30 mg once daily for up to 4 weeks **Oesophagitis due to GORD:** 30 mg once daily for 4 weeks, repeat course possibly necessary **GORD reflux prevention:** Maintenance 15 mg once daily for maximum 1 year **Functional dyspepsia**: 15-30 mg once daily for 2-4 weeks	Capsules	1-2 hours	Metabolites mainly excreted in the faeces Urine 30-50 %	Short-term treatment • Gastric/duodenal ulcers • Reflux oesophagitis • In conjunction with appropriate antibiotics as part of eradication programme for *H. pylori* positive duodenal ulcer
Omeprazole	**Oral:** Adults **Duodenal ulcer:** 20 mg daily for 2-4 weeks. Patients refractory to other treatment regimens, 40 mg once daily **Relapse prevention and *H. pylori* positive duodenal ulcer:** 10 mg once daily, increase to 20-40 mg daily if necessary. Administer as part of eradication programme with appropriate antibiotic for *H. pylori* associated ulcers **Gastric ulcer and reflux oesophagitis:** 20 mg daily for 4-8 weeks. When refractory to other treatment regimens 40 mg once daily **Long-term reflux oesophagitis:** 10 mg once daily, increase to 20-40 mg daily if necessary. If severe or recurrent, continue with 20 mg daily **NSAID associated gastro-duodenal lesions:** 20 mg once daily for 4 weeks, continue for further 4 weeks if full healing not initially achieved **NSAID associated prophylaxis:** 20 mg once daily **Symptomatic GORD:** 10-20 mg daily for 4 weeks **Functional dyspepsia:** 20 mg once daily. If no symptom control after 4 weeks investigate further	Capsules MUPS Tablets Injection	0,5-3 hours	Metabolites mainly excreted in urine	**Oral:** Adults: • Duodenal ulcers including relapse prevention • Gastric ulcers • Reflux oesophagitis including long-term management • Zollinger-Ellis syndrome • Symptomatic heartburn relief in GORD • Short-term relief of functional dyspepsia • Duodenal ulcers associated with *H. pylori* infection • NSAID associated gastric/duodenal ulcer and reduce the risk of developing/relapse of such associated ulcer Children: • Short-term treatment of severe ulcerative reflux oesophagitis resistant to previous treatment

Proton pump inhibitors (PPIs) (continued)

Generic name[1-5]	Usual dosage range[1,3,4,6]	Dosage forms[1,3,4]	Half life[2]	Elimination[2]	Therapeutic area[1-5]
Omeprazole (continued)	**Zollinger-Ellison syndrome:** 60 mg once daily, individualise continue as long as needed. Doses > 80 mg administer in 2 divided doses Paediatric **Severe ulcerative GORD in children ≥ 1 year:** 10-20 kg: 10 mg once daily. > 20 kg: 20-40 mg once daily **IV:** Administer as IV infusion of 40 mg as daily dose over 20-30 minutes Divide dose into two daily infusions if the dose exceeds 60 mg per day				**IV:** Adult: • Short-term treatment of duodenal ulcers, gastric ulcers, reflux oesophagitis and Zollinger-Ellison syndrome when oral therapy or contra-indicated
Pantoprazole	**Oral:** **Mild GORD:** 20 mg daily for 4 weeks, continue for 4 weeks if not sufficiently healed **Long-term management and prevention of GORD relapse:** 20 mg daily, increase to 40 mg if relapse occurs, reduce back to 20 mg daily after relapse has healed **Duodenal ulcer:** 40 mg once daily for 2-4 weeks **Gastric ulcer and reflux oesophagitis:** 40 mg daily for 4-8 weeks **Zollinger-Ellison syndrome:** Initiate 80 mg daily, thereafter titrate up or down as needed, dosage above 80 mg to be divided and administered twice daily **NSAID induced gastro-duodenal lesions and dyspeptic syndrome prevention:** 20 mg daily **IV:** Administer over 2-15 min **Duodenal ulcer:** 40 mg once daily for 2-4 weeks **Gastric ulcer and reflux oesophagitis:** 40 mg once daily 4-8 weeks **Zollinger-Ellison syndrome:** Initially 80 mg daily, thereafter titrate up or down as needed, dosage above 80 mg to be divided and administered twice daily	Tablets Injection	1 hour	Metabolites excreted mainly in urine	**Oral:** • Short-term treatment of duodenal and gastric ulcer • Reflux oesophagitis • Duodenal ulcer associated with *H. pylori* infection in combination with appropriate antibiotic • Zollinger-Ellison syndrome • Prevention of NSAID induced gastro-duodenal lesions and dyspeptic symptoms. **IV:** • Short-term treatment of duodenal and gastric ulcers • Reflux oesophagitis • Duodenal ulcers associated with *H. pylori* in combination with appropriate antibiotics • Zollinger-Ellison syndrome
Rabeprazole	Adults **Active duodenal ulcer/active benign gastric ulcer:** 20 mg daily, for 4-6 weeks, continue for additional 4-6 weeks if required to achieve healing **Erosive/ulcerative GORD:** 20 mg daily, for 4-8 weeks **GORD maintenance:** 10-20 mg daily for maximum 12 months **Symptomatic GORD:** 10 mg daily without oesophagitis, investigate further if control not achieved in 4 weeks, once symptoms resolved administer 10 mg daily when needed **Zollinger-Ellison syndrome and other hypersecretory conditions:** 60 mg daily, titrate to 120 mg based on individual needs, divide 120 mg dose into 60 mg twice daily, continue treatment as long as clinically indicated	Tablets	1 hour	Metabolites excreted mainly in urine	• Active duodenal and benign gastric ulcer • Symptomatic erosive/ulcerative GORD • Maintenance therapy of erosive/ ulcerative GORD • Symptomatic therapy of GORD • Zollinger-Ellison syndrome and other pathological hypersecretory conditions • *H. pylori* positive duodenal ulcer with appropriate antibiotic

References:

1. Snyman JR, editor. Monthly Index of Medical Specialities (MIMS). April 2013 ed. Johannesburg: Times Media; 2013.
2. Sweetman SC, editor. Martindale: The Complete Drug Reference. 36th ed. London: Pharmaceutical Press; 2009.
3. Emims electronic database. Prothiaden. Assessed 18 Feb. 14
4. Snyman JR, editor. MIMS Desk Reference. Volume 46 2011 ed. Rosebank, South Africa: Times Media; 2011.
5. Open Data Drug and Drug Target Database www.drugbank.ca
6 BPrilosec®: Highlights of prescribing information. Available from http://www1.astrazeneca-us.com/pi/Prilosec.pdf