

ANNEX 1

Drug information sheets

Adapted from *Drug-resistant tuberculosis: a survival guide for clinicians*. San Francisco, Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004

Common presentations of the drugs are described; actual preparations may vary depending on manufacturer.

AMIKACIN (Am)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism

Bactericidal: aminoglycosides inhibit protein synthesis through disruption of ribosomal function; less effective in acidic, intracellular environments; polypeptides appear to inhibit translocation of the peptidyl-tRNA and the initiation of protein synthesis; aminoglycosides are not metabolized in the liver, they are excreted unchanged in the urine.

Preparation and dose

Amikacin sulfate, colourless solution; 250 mg/ml (2 or 4 ml vials) and 50 mg/ml (2 ml vial). The optimal dose is 15–20 mg/kg body weight, usually 750 mg to 1 g given daily or 5–6 days per week, by deep intramuscular injection. Rotation of injection sites avoids local discomfort. When necessary, it is possible to give the drug at the same total dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects.

Storage

Solution is stable at room temperature (15–25 °C); diluted solution is stable at room temperature for at least 3 days or in the refrigerator for at least 60 days.

Oral absorption

There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.

CSF penetration

Penetrates inflamed meninges only.

Special circumstances

Pregnancy/breastfeeding: safety class D. No reports linking the use of amikacin to congenital defects have been located. Ototoxicity has not been reported as an effect of in utero exposure to amikacin; however, eighth cranial nerve toxicity in the fetus is well known following exposure to other aminoglycosides (kanamycin and streptomycin) and could potentially occur with amikacin. Only a trace amount of amikacin was found in some nursing infants. Given the poor absorption of aminoglycosides, systemic toxicity should not occur, but alteration in normal bowel flora may occur in nursing infants.

Renal disease: use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg 2 or 3 times per week) is recommended for creatinine clearance <30 ml/min or haemodialysis.

AMIKACIN (Am)**DRUG CLASS: AMINOGLYCOSIDE**

Special circumstances	Hepatic disease: drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution – some patients with severe liver disease may progress rapidly to hepatorenal syndrome.
Adverse effects	<p>Frequent: pain at injection site, proteinuria, serum electrolyte disturbances including hypokalaemia and hypomagnesaemia.</p> <p>Occasional: cochlear ototoxicity (hearing loss, dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, often irreversible), peripheral neuropathy, rash, vestibular toxicity (nausea, vomiting, vertigo, ataxia, nystagmus), eosinophilia.</p> <p>Ototoxicity potentiated by certain diuretics (especially loop diuretics), advanced age, and prolonged use. The effect of non-depolarizing muscle relaxants may be increased. Penicillins: in vitro antagonism.</p>
Drug interactions	<p>Loop diuretics (bumetanide, furosemide, etacrynic acid, torasemide). Co-administration of aminoglycosides with loop diuretics may have an additive or synergistic auditory ototoxicity. Ototoxicity appears to be dose-dependent and may be increased with renal dysfunction. Irreversible ototoxicity has been reported. Avoid concomitant administration; if used together, careful dose adjustments in patients with renal failure and close monitoring for ototoxicity are required.</p> <p>Non-depolarizing muscle relaxants (atracurium, pancuronium, tubocurarine, gallamine triethiodide): possible enhanced action of non-depolarizing muscle relaxants resulting in possible respiratory depression. Nephrotoxic agents (amphotericin B, foscarnet, cidofovir): additive nephrotoxicity.</p> <p>Penicillins: in vitro inactivation (possible). Do not mix together before administration.</p>
Contraindications	Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular, or auditory impairment.
Monitoring	Monthly creatinine and serum potassium in low-risk patients (young with no co-morbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.
Alerting symptoms	<ul style="list-style-type: none"> — Problems with hearing, dizziness or balance — Rash or swelling of the face — Trouble breathing — Decreased urination — Swelling, pain or redness at IM site — Muscle twitching or weakness

CAPREOMYCIN (Cm)	
DRUG CLASS: CYCLIC POLYPEPTIDE	
Activity against TB, mechanism of action, and metabolism	Bactericidal: capreomycin has a different chemical structure from the aminoglycosides, but the mechanism of antibacterial activity is similar. Polypeptides appear to inhibit translocation of the peptidyl-tRNA and the initiation of protein synthesis. No cross-resistance with the aminoglycosides. 50–60% excreted via glomerulofiltration. Small amount of biliary excretion.
Preparation and dose	Capreomycin sulfate is supplied as a sterile white powder for intramuscular injection in sealed vials each containing 1000 units, approximately equivalent to 1 g capreomycin base. This should be dissolved in 2 ml of 0.9% sodium chloride in water; 2–3 minutes should be allowed for complete solution. Dose: 15–20 mg/kg daily. The usual dose is 1 g in a single dose daily. When necessary, it is possible to give the drug at the same dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects.
Storage	Reconstituted capreomycin can be stored in the refrigerator for up to 24 hours before use.
Oral absorption	There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
CSF penetration	Penetrates inflamed meninges only.
Special circumstances	Pregnancy/breastfeeding: less ototoxicity reported in adults with capreomycin than with aminoglycosides; unknown if these data can be extrapolated to the developing fetal ear. Category C animal studies show teratogenic effect (“wavy ribs” when given 3.5 times the human dose). Avoid in pregnancy. Concentrations in breast milk unknown. Renal disease: use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg 2 or 3 times per week) is recommended for creatinine clearance <30 ml/min or haemodialysis.
Adverse effects	Frequent: nephrotoxicity (20–25%), tubular dysfunction, azotemia, proteinuria, urticaria or maculopapular rash. Occasional: ototoxicity (vestibular>auditory); electrolyte abnormalities (decreased blood levels of calcium, magnesium, and potassium); pain, induration and sterile abscesses at injection sites.
Drug interactions	Avoid co-administration of non-depolarizing muscle relaxants. If concurrent administration is needed, titrate the non-depolarizing muscle relaxant slowly and monitor neuromuscular function closely. Though not reported with capreomycin, neuromuscular blockade has been reported with other polypeptide antibiotics when administered with non-depolarizing muscle relaxants. Avoid use with other nephro- or ototoxic agents because of the additive effect.
Contraindications	Patients with hypersensitivity to capreomycin. Great caution must be exercised in patients with renal insufficiency or pre-existing auditory impairment.

CAPREOMYCIN (Cm)**DRUG CLASS: CYCLIC POLYPEPTIDE**

Monitoring	Monthly creatinine and serum potassium in low-risk patients (young with no co-morbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Electrolyte disturbances are more common with capreomycin than other injectable agents. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.
Alerting symptoms	<ul style="list-style-type: none"> — Rash — Decreased urination — Fever or chills — Trouble breathing — Bleeding or bruising — Muscle weakness — Problems with hearing, dizziness or balance — Bleeding or lump at IM injection site

CIPROFLOXACIN (Cfx)	
DRUG CLASS: FLUOROQUINOLONE	
Activity against TB, mechanism of action, and metabolism	Bactericidal: acts by inhibiting the A subunit of DNA gyrase (topoisomerase), which is essential in the reproduction of bacterial DNA. There is no cross-resistance with other antituberculosis agents, but near complete cross-resistance between ofloxacin and ciprofloxacin and high in vitro cross-resistance with moxifloxacin and gatifloxacin. Ciprofloxacin is eliminated principally by urinary excretion, but non-renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa.
Preparation and dose	Tablets (250, 500, 1000 mg). Vials (20 and 40 ml) or flexible containers (200 and 400 ml) with aqueous or 5% dextrose IV solutions equivalent to 200 and 400 mg. Usual dose: 1000–1500 mg/day.
Storage	Room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	Well absorbed (70–85%) from the gastrointestinal tract and may be taken with meals or on an empty stomach. Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, zinc, vitamins, didanosine, sucralfate).
Distribution, CSF penetration	Widely distributed to most body fluids and tissues; high concentrations are attained in kidneys, gall bladder, gynaecological tract, liver, lung, prostatic tissue, phagocytic cells, urine, sputum, and bile, skin, fat, muscle, bone and cartilage. CSF penetration is 5–10% and with inflamed meninges 50–90%.
Special circumstances	Pregnancy/breastfeeding: safety class C. Ciprofloxacin levels in amniotic fluid and breast milk almost as high as in serum. Fluoroquinolones are not recommended during breastfeeding because of the potential for arthropathy. Animal data demonstrated arthropathy in immature animals, with erosions in joint cartilage. Renal disease: doses of ciprofloxacin should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/min, the recommended dosing is 1000–1500 mg 3 times per week.
Adverse effects	Generally well tolerated. Occasional: gastrointestinal intolerance; CNS-headache, malaise, insomnia, restlessness, and dizziness. Rare: allergic reactions; diarrhoea; photosensitivity; increased liver function tests (LFTs); tendon rupture; peripheral neuropathy.
Drug interactions	Sucralfate: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate. Antacids (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy. Probenecid: interferes with renal tubular secretion of ciprofloxacin; this may result in 50% increase in serum level of ciprofloxacin. Milk or dairy products: decrease the gastrointestinal absorption of ciprofloxacin by 36–47%. Vitamins and minerals containing divalent and trivalent cations such as zinc and iron: formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.

CIPROFLOXACIN (Cfx)	
DRUG CLASS: FLUOROQUINOLONE	
Drug interactions	<p>Mexiletine: fluoroquinolones may inhibit cytochrome P450 1A2 resulting in increased mexiletine concentration.</p> <p>Warfarin: case reports of ciprofloxacin enhancing anticoagulation effect of warfarin.</p>
Contraindications	Pregnancy, intolerance of fluoroquinolones.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	<ul style="list-style-type: none"> — Pain, swelling or tearing of a tendon or muscle or joint pain — Rashes, hives, bruising or blistering, trouble breathing — Diarrhoea — Yellow skin or eyes — Anxiety, confusion or dizziness

CLOFAZIMINE (Cfz)	
DRUG CLASS: PHENAZINE DERIVATIVE	
Activity against TB, mechanism of action, and metabolism	Bacteriostatic against <i>M. leprae</i> , active in vitro against <i>M. tuberculosis</i> . Clinical effectiveness against <i>M. tuberculosis</i> not well established. Clofazimine appears to bind preferentially to mycobacterial DNA (principally at base sequences containing guanine) and inhibit mycobacterial replication and growth. Excreted in faeces as unabsorbed drug and via biliary elimination. Little urinary excretion.
Preparation and dose	Capsules (50 and 100 mg).
Storage	Store below 30 °C, in airtight containers.
Oral absorption	20–70% absorbed from from gastrointestinal tract.
Distribution, CSF penetration	Widely distributed principally to fatty tissue, reticuloendothelial system and macrophages. High concentrations found in mesenteric lymph nodes, adipose tissue, adrenals, liver, lungs, in gall bladder, bile and spleen.
Special circumstances	Pregnancy/breastfeeding: safety class C. Animal studies demonstrated teratogenicity (retardation of fetal skull ossification). Crosses placenta and is excreted in milk. Not recommended during breastfeeding. Renal disease: usual dose. Hepatic disease: dose adjustments should be considered in patients with severe hepatic insufficiency.
Adverse effects	Frequent: ichthyosis, and dry skin; pink to brownish-black discoloration of skin, cornea, retina and urine; anorexia and abdominal pain.
Drug interactions	May decrease absorption rate of rifampicin. Isoniazid increases clofazimine serum and urine concentrations and decreases skin concentrations. Ingestion of clofazimine with orange juice resulted in a modest reduction in clofazimine bioavailability.
Contraindications	Pregnancy, severe hepatic insufficiency, hypersensitivity to Cfz.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	— Nausea and vomiting — Abdominal pain/distress (caused by crystal depositions and can present as an acute abdomen)

CYCLOSERINE (Cs)	
DRUG CLASS: ANALOG OF D-ALANINE	
Activity against TB, mechanism of action, and metabolism	Bacteriostatic: competitively blocks the enzyme that incorporates alanine into an alanyl-alanine dipeptide, an essential component of the mycobacterial cell wall. No cross-resistance with other antituberculosis drugs. 60–70% excreted unchanged in the urine via glomerular filtration; small amount excreted in faeces; small amount metabolized.
Preparation and dose	Capsules (250 mg). 10–15 mg/kg daily (max. 1000 mg), usually 500–750 mg per day given in two divided doses. (Some producers of terizidone make 300 mg capsule preparations, while others make 250 mg.)
Storage	Room temperature (15–25 °C) in airtight containers.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); 70–90% absorbed.
Distribution, CSF penetration	Widely distributed into body tissue and fluids such as lung, bile, ascitic fluid, pleural fluid, synovial fluid, lymph, sputum. Very good CSF penetration (80–100% of serum concentration attained in the CSF, higher level with inflamed meninges)
Special circumstances	Pregnancy/breastfeeding: safety class C. Breastfeeding with B ₆ supplement to the infant. Renal disease: doses of cycloserine should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 250 mg/day, or 500 mg/dose 3 times per week. The appropriateness of 250 mg/day doses has not been established. There should be careful monitoring for evidence of neurotoxicity; if possible, measure serum concentrations and adjust regimen accordingly.
Adverse effects	Frequent: neurological and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache, drowsiness. Occasional: Visual changes; skin rash; numbness, tingling or burning in hands and feet; jaundice; eye pain. Rare: seizures, suicidal thoughts.
Drug interactions	Ethionamide: additive nervous system side-effects. Isoniazid: additive nervous system side-effects. Phenytoin: may increase phenytoin levels. Toxic effect if combined with alcohol, increases risk of seizures. Vitamin B ₆ decreases CNS effect.
Contraindications	Hypersensitivity to cycloserine. Epilepsy. Depression, severe anxiety or psychosis. Severe renal insufficiency. Excessive concurrent use of alcohol.
Monitoring	When available, serum drug monitoring to establish optimal dosing (not higher than 30 µg/ml).
Alerting symptoms	<ul style="list-style-type: none"> — Seizures — Shakiness or trouble talking — Depression or thoughts of intentional self-harm — Anxiety, confusion or loss of memory — Personality changes, such as aggressive behaviour — Rash or hives — Headache

ETHIONAMIDE (Eto)
PROTIONAMIDE (Pto)
DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID

Activity against TB, mechanism of action, and metabolism	Bacteriostatic: the mechanism of action of thionamides has not been fully elucidated, but they appear to inhibit mycolic acid synthesis. Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and protionamide (partial cross-resistance with thioacetazone). Ethionamide is extensively metabolized, probably in the liver, to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.
Preparation and dose	Ethionamide and protionamide are normally administered in the form of tablets containing 125 mg or 250 mg of active drug. The maximum optimum daily dose is 15–20 mg/kg/day (max. 1 g/day), usually 500–750 mg.
Storage	Room temperature (15–25 °C), in airtight containers.
Oral absorption	100% absorbed but sometimes erratic absorption caused by gastrointestinal disturbances associated with the medication.
Distribution, CSF penetration	Rapidly and widely distributed into body tissues and fluids, with concentrations in plasma and various organs being approximately equal. Significant concentrations also are present in CSF.
Special circumstances	<p>Pregnancy/breastfeeding: safety class C. Animal studies have shown ethionamide to be teratogenic. Newborns who are breastfed by mothers who are taking ethionamide should be monitored for adverse effects.</p> <p>Renal disease: doses of the thionamides are only slightly modified for patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 250–500 mg daily.</p> <p>Hepatic disease: thionamides should not be used in severe hepatic impairment.</p> <p>Porphyria: ethionamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals and in vitro systems.</p>
Adverse effects	<p>Frequent: severe gastrointestinal intolerance (nausea, vomiting, diarrhoea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia and weight loss). Adverse gastrointestinal effects appear to be dose-related, with approximately 50% of patients unable to tolerate 1 g as a single dose. Gastrointestinal effects may be minimized by decreasing dosage, by changing the time of drug administration, or by the concurrent administration of an antiemetic agent.</p> <p>Occasional: allergic reactions; psychotic disturbances (including depression), drowsiness, dizziness, restlessness, headache, and postural hypotension. Neurotoxicity (administration of pyridoxine has been recommended to prevent or relieve neurotoxic effects); transient increases in serum bilirubin; reversible hepatitis (2%) with jaundice (1–3%); gynaecomastia; menstrual irregularity, arthralgias, leukopenia, hypothyroidism especially when combined with PAS.</p> <p>Rare: reports of peripheral neuritis, optic neuritis, diplopia, blurred vision, and a pellagra-like syndrome, reactions including rash, photosensitivity, thrombocytopenia and purpura.</p>

ETHIONAMIDE (Eto)
PROTIONAMIDE (Pto)
DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID

Drug interactions	<p>Cycloserine: potential increase incidence of neurotoxicity.</p> <p>Ethionamide has been found to temporarily raise serum concentrations of isoniazid. Thionamides may potentiate the adverse effects of other antituberculosis drugs administered concomitantly. In particular, convulsions have been reported when ethionamide is administered with cycloserine. Excessive ethanol ingestion should be avoided because of possible psychotic reaction.</p> <p>PAS: possible increase in liver toxicity, monitor liver enzymes; hypothyroidism in case of combined administration.</p>
Contraindications	Thionamides are contraindicated in patients with severe hepatic impairment and in patients who are hypersensitive to these drugs.
Monitoring	Ophthalmological examinations should be performed before and periodically during therapy. Periodic monitoring of blood glucose and thyroid function is desirable. Diabetic patients should be particularly alert for episodes of hypoglycaemia. Liver function tests should be carried out before and during treatment with ethionamide.
Alerting symptoms	<ul style="list-style-type: none"> — Any problems with eyes: eye pain, blurred vision, color blindness, or trouble seeing — Numbness, tingling, or pain in hands and feet — Unusual bruising or bleeding — Personality changes such as depression, confusion or aggression — Yellowing of skin — Dark-coloured urine — Nausea and vomiting — Dizziness