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Medication Fact Sheets

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AMIKACIN (AK) [1 of 2]

Drug class	Aminoglycoside
Trade name	Amikacin/Amikin
Activity against TB	Bactericidal; has strong anti-TB activity. Cross-resistance with kanamycin and some data suggesting cross-resistance with capreomycin.
Cross-resistance	Kanamycin; variable frequency of cross-resistance with capreomycin has been reported
Dose (all once daily)	<p>Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week 15 mg/kg/dose, 2–3 times per week can be used after culture conversion is documented after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations).</p> <p>> 59 yrs of age: Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week</p> <p>Children: 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 3 days per week after initial period daily.</p> <p>Renal failure/dialysis: 12–15 mg/kg/dose after dialysis 2-3 times weekly (not daily).</p> <p>Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p>For dosing, use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft</p> <p><i>Concentrations should be followed closely.</i></p>
Route of administration	IV or IM (intraperitoneal and intrathecal have been reported—penetrates meninges only with inflammation). Some report that it is more painful than IM streptomycin. Not absorbed orally.
Preparation	Colorless solution; 250 mg/ml (2, 3, or 4 ml vials) and 50 mg/ml (2 ml vial). For intravenous solution, mix with D5W or other solutions (in at least 100 ml of fluid for adults or 5 mg/ml for children).
Storage	Solution in original vial is stable at room temperature; diluted solution is stable at room temperature at least 3 weeks or in the refrigerator at least 60 days.
Pharmacokinetics	<p>For intravenous administration, infuse over 30-60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak concentrations are achieved at 1–2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p>Peak concentrations for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p>Peak concentrations of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations are generally < 5 mcg/ml in patients with normal renal function.</p>
Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.

AMIKACIN (AK) [2 of 2]

CSF penetration	Variable penetration; appears to penetrate inflamed meninges better.
Special circumstances	<p>Use in pregnancy/breastfeeding: Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding.</p> <p>Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See “Dose – Renal Failure/Dialysis” (previous page). The drug is variably cleared by hemodialysis.</p> <p>Use in hepatic disease: Drug concentrations 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 hepato-renal syndrome.</p> <p>Diuretic use: Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</p>
Adverse reactions	<p>Nephrotoxicity: 9% for general population (may be lower for once-daily use, higher for prolonged use).</p> <p>Ototoxicity (hearing loss): Increased with advanced age and prolonged use.</p> <p>Vestibular toxicity.</p> <p>Local pain with IM injections.</p> <p>Electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia.</p>
Contraindications	<p>Pregnancy — relative contraindication (congenital deafness seen with streptomycin and kanamycin use in pregnancy).</p> <p>Hypersensitivity to aminoglycosides.</p> <p>Caution with renal, hepatic, vestibular, or auditory impairment.</p>
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium, and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
2012 wholesale cost 30-day supply, 60-kg person	\$176 (outpatient public health pricing) \$324 (community hospital)
Patient instructions	<p>Call your doctor right away if you have:</p> <ul style="list-style-type: none"> • Problems with hearing, dizziness, or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Swelling, pain, or redness at your IV site • Muscle twitching or weakness

AMOXICILLIN/CLAVULANATE (AMX/CLV) [1 of 2]

Drug class	Penicillin/beta-lactam inhibitor
Trade name	Augmentin XR or Augmentin ES-600 suspension
Activity against TB	Conflicting and limited reports, but possible early bactericidal activity.
Cross-resistance	None reported
Dose	<p>Adults: 2000 mg as amoxicillin/125 mg clavulanate twice daily.</p> <p>Children: 80 mg/kg/day divided twice daily of the amoxicillin component.</p> <p>Renal failure/dialysis: For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin twice daily; for creatinine clearance < 10 ml/min dose 1000 mg as amoxicillin once daily.</p> <p>Hemodialysis: Single dose every 24 hours and after each dialysis session.</p>
Route of administration	Oral. Imipenem/cilastatin should be used if a parenteral beta-lactam drug is desired.
Preparation	For adults: 1000 mg amoxicillin/62.5 mg clavulanate (Augmentin XR) tablets, 2 tablets twice daily; for pediatric dosing: 600 mg/5ml product (Augmentin ES-600). A less expensive equivalent can be achieved by prescribing generic amoxicillin/clavulanate and additional amoxicillin to achieve the same total daily dose of amoxicillin and clavulanate (for adults: 4000 mg amoxicillin and 250 mg clavulanate divided twice daily).
Storage	Tablets are stable at room temperature; reconstituted suspension should be stored in the refrigerator and discarded after 10 days.
Pharmacokinetics	<p>Time to peak oral concentration is 60–90 minutes.</p> <p>Serum concentrations of 17 mcg/ml of amoxicillin were reported following a 2000 mg (as amoxicillin) dose.</p>
Oral absorption	Good oral absorption, best tolerated and well absorbed when taken at the start of a standard meal.
CSF penetration	Approximately 5% of the plasma concentration reaches the CSF.
Special circumstances	<p>Use in pregnancy/breastfeeding: Probably safe in pregnancy (no known risk); can be used while breastfeeding.</p> <p>Use in renal disease: Amoxicillin is renally excreted and the dose should be adjusted for renal failure. It is cleared by dialysis, so should be dosed after dialysis (see above).</p> <p>Use in hepatic disease: Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure.</p>
Adverse reactions	<p>Diarrhea and abdominal discomfort are most common.</p> <p>Hypersensitivity.</p> <p>Nausea, vomiting, and rash are also common.</p> <p>Rare side effects have been reported in all other organ systems.</p>

AMOXICILLIN/CLAVULANATE (AMX/CLV) [2 of 2]

Contraindications	Penicillin allergy; use with caution with cephalosporin allergies.
Monitoring	No specific monitoring is required.
2012 wholesale cost 30-day supply, 60-kg person	\$241 (outpatient public health pricing) \$294 (community hospital)
Patient instructions	<p>Take at the beginning of a meal.</p> <p>Store tablets at room temperature; store suspension in the refrigerator—throw away after 10 days and refill the prescription.</p> <p>Call your doctor right away if you have:</p> <ul style="list-style-type: none">• Rash or swelling• Trouble breathing• Severe diarrhea

BEDAQUILINE (BDQ) [1 of 2]

Drug class	Diarylquinolone									
Trade name	Sirturo									
Activity against TB	Bactericidal; has strong anti-TB activity. Inhibits adenosine 5'-triphosphate (ATP) synthase with <i>in vitro</i> activity against both replicating and nonreplicating bacilli.									
Cross-resistance	Cross-resistance with clofazimine has been demonstrated in both directions through efflux-based resistance.									
Dose	<p>Adults: 400 mg daily for 14 days, followed by 200 mg 3 times weekly for 22 weeks. Has not been studied past 24 weeks of administration.</p> <p>Missed doses: After the first 2 weeks of treatment, the dose changes to the 200 mg three times per week, even if doses were missed during the first 2 weeks. Patients should not make up for missed doses during the first 2 weeks of treatment.</p> <p>Concomitant medications: Bedaquiline is metabolized by CYP3A4 and co-administration of rifamycins (e.g., rifampin, rifapentine and rifabutin) or other strong CYP3A4 inducers may require dose adjustment. See Section 7 in http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf.</p> <p>Children: Has not been studied in children. Based strictly on weight, converting from the adult doses in a 70 kg patient, estimated pediatric doses would be 6 mg/kg daily for 14 days, followed by 3 mg/kg 3times weekly for 22 weeks. However, these doses are not supported by clinical experience.</p> <p>Renal failure/dialysis: No dose adjustment needed for mild to moderate renal insufficiency, but should be used with caution in patients requiring renal dialysis.</p>									
Route of administration	Oral.									
Preparation	100 mg tablets.									
Storage	Store at room temperature. Tablets removed from the original packaging should be stored in a tight, light-resistant container and labeled with an expiration date not to exceed 3 months.									
Pharmacokinetics	<p>Peak oral absorption occurs approximately 5 hours post dose. Administration with a standard meal increases bioavailability about 2-fold, therefore drug should be taken with food. The drug is highly protein-bound. Bedaquiline has a mean terminal half-life of 5.5 months. This likely reflects slow release from peripheral tissues.</p> <p>Peak concentrations typically occur 5-6 hours after the dose is given. Serum concentrations are not clinically available.</p> <p>Peak concentrations depend on the size and number of doses:</p> <table border="1"> <thead> <tr> <th>Dose (daily)</th> <th>N doses</th> <th>C_{max} (mcg/ml)</th> </tr> </thead> <tbody> <tr> <td>200 mg</td> <td>14th dose</td> <td>2.7 (1.7-4.3)</td> </tr> <tr> <td>400 mg</td> <td>14th dose</td> <td>4.5 (2.4-13.6)</td> </tr> </tbody> </table>	Dose (daily)	N doses	C _{max} (mcg/ml)	200 mg	14th dose	2.7 (1.7-4.3)	400 mg	14th dose	4.5 (2.4-13.6)
Dose (daily)	N doses	C _{max} (mcg/ml)								
200 mg	14th dose	2.7 (1.7-4.3)								
400 mg	14th dose	4.5 (2.4-13.6)								
Oral absorption	Good oral absorption. Should be given with a meal to increase bioavailability.									
CSF penetration	No data available. Also, there are no data on the treatment of extra-pulmonary TB (e.g., central nervous system) with bedaquiline.									

BEDAQUILINE (BDQ) [2 of 2]

<p>Special circumstances</p>	<p>Use in pregnancy/breastfeeding: Pregnancy category B. No fetal harm found in animal studies. The drug is concentrated in breast milk and avoiding nursing should be considered.</p> <p>Use in renal disease: No dose adjustment needed for mild to moderate renal insufficiency but should be used with caution in patients requiring peritoneal or hemodialysis. Drug level monitoring may be useful, once available.</p> <p>Use in hepatic disease: No dose adjustment is necessary for bedaquiline in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and should be used with caution in these patients, and only when the benefits outweigh the risks. Clinical monitoring for bedaquiline -related adverse reactions is recommended.</p>
<p>Adverse reactions</p>	<p>QTc prolongation, hepatitis, nausea, joint pain, headache, elevated amylase, coughing up blood, chest pain, loss of appetite, and/or rash.</p>
<p>Contraindications</p>	<p>None, but use with caution if other QTc prolonging agents, such as clofazimine or fluoroquinolones, are being given.</p>
<p>Monitoring</p>	<p>EKG at baseline, 2, 12 and 24 weeks of treatment. Stop bedaquiline if QTc > 500 and monitor EKGs frequently until QTc returns to normal. Baseline potassium, calcium and magnesium, repeat if QTc prolongation occurs, and monthly if on injectable drug. Baseline and monthly LFTs.</p>
<p>Warning</p>	<p>An increased risk of death was seen in the bedaquiline treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. There was no pattern to the causes of death, and cause and effect could not be established. Only use bedaquiline when an effective treatment regimen cannot otherwise be provided.</p> <p>QTc prolongation can occur with bedaquiline. Use with drugs that prolong the QTc interval may cause additive QTc prolongation.</p>
<p>2014 wholesale cost 24-week supply, 60-kg person</p>	<p>\$23,070 (outpatient public health pricing) \$30,000 (community hospital)</p>
<p>Patient instructions</p>	<p>Avoid alcohol. Take medication with food</p> <p>Call your doctor and stop the medicine right away if you have:</p> <ul style="list-style-type: none"> • serious heart rhythm changes (QTc prolongation). Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. • liver problems (hepatotoxicity). Call your healthcare provider right away if you have unexplained symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light-colored bowel movements, dark-colored urine, yellowing of your skin or the white of your eyes.

CAPREOMYCIN (CM) [1 of 2]

Drug class	Cyclic polypeptide
Trade name	Capastat
Activity against TB	Bactericidal; has strong anti-TB activity; inhibits protein synthesis. Some data suggesting cross-resistance with amikacin and kanamycin.
Cross-resistance	Amikacin and kanamycin. Variable frequency of cross-resistance has been reported.
Dose (all once daily)	<p>Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week 15 mg/kg/dose, 2–3 times per week after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations).</p> <p>> 59 yrs of age: Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week.</p> <p>Children: 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 2–3 days per week after initial period daily.</p> <p>Renal failure/dialysis: 12–15 mg/kg/dose 2–3 times weekly (not daily).</p> <p>Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p>For dosing, use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft <i>Concentrations should be followed closely.</i></p>
Route of administration	IV or IM.
Preparation	Capreomycin is available in vials of 1 gram for either IM or IV administration. The contents of the vial should be reconstituted with 2 ml or more of NS or sterile water.
Storage	Package insert indicates that reconstituted capreomycin can be stored in the refrigerator up to 24 hours prior to use. Other data suggest that it may be held for 14 days in the refrigerator or 2 days at room temperature.
Pharmacokinetics	<p>Intramuscular peak concentrations are achieved at 2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p>Peak concentrations for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p>Peak concentrations of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations should be < 5 mcg/ml in patients with normal renal function.</p>
Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.
CSF penetration	There is a paucity of data regarding capreomycin's penetration of the meninges.

CAPREOMYCIN (CM) [2 of 2]

<p>Special circumstances</p>	<p>Use in pregnancy/breastfeeding: Generally avoided in pregnancy due to congenital deafness seen with streptomycin and kanamycin. There are case reports of its safe use in pregnancy (unaffected newborns). Can be used while breastfeeding.</p> <p>Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See “Dose – Renal Failure/Dialysis” (previous page) and Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p> <p>Use in hepatic disease: Drug concentrations 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 hepato-renal syndrome.</p>
<p>Adverse reactions</p>	<p>Similar to the aminoglycosides.</p> <p>Nephrotoxicity: 20%–25% including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium.</p> <p>Ototoxicity (hearing loss): Occurs more often in elderly persons or those with pre-existing renal impairment; vestibular toxicity.</p> <p>Local pain with IM injections.</p> <p>Electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia.</p> <p>Liver function test abnormalities when used with other TB drugs.</p>
<p>Contraindications</p>	<p>Hypersensitivity to capreomycin. Some experts would not use capreomycin if vestibular side effects resulted from aminoglycoside use.</p> <p>Generally avoided in pregnancy due to congenital deafness seen with aminoglycosides and mechanism of ototoxicity may be similar with capreomycin. There are case reports of its safe use in pregnancy (unaffected newborns).</p>
<p>Monitoring</p>	<p>Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium, and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor capreomycin concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.</p>
<p>2012 wholesale cost 30-day supply, 60-kg person</p>	<p>\$349 (outpatient public health pricing) \$3,598 (community hospital)</p>
<p>Patient instructions</p>	<p>Call your doctor right away if you have:</p> <ul style="list-style-type: none"> • Rash • Fever or chills • Bleeding or bruising • Problems with hearing, dizziness, or balance • Bleeding or a lump where the shot is given • Decreased urination • Trouble breathing • Muscle weakness

CLARITHROMYCIN (CLR) [1 of 2]

Drug class	Macrolide
Trade name	Biaxin
Activity against TB	Much more active against nontuberculous mycobacteria, especially MAC, but some isolates of TB are susceptible <i>in vitro</i> . Does not have proven value for the treatment of TB in humans, and <i>in vitro</i> data are not particularly encouraging. Inhibits protein synthesis by binding to the 50S ribosomal subunit.
Cross-resistance	None reported.
Dose	Adults: 500 mg twice daily or 1 gram daily of extended release formulation Children: 7.5 mg/kg q 12 hours up to 500 mg Renal failure/dialysis: The drug is cleared both hepatically and renally. In severe renal impairment, the interval between doses should be increased, i.e., 500 mg daily.
Route of administration	Oral
Preparation	Oral tablets of 250 and 500 mg. Also available in Extended Release tablets for once daily use. Oral suspension 125 mg/5 ml and 250 mg/5 ml.
Storage	Store tablets and unmixed granules for suspension at room temperature in a well sealed container and protect from light. The mixed suspension should not be refrigerated and can be stored for 14 days.
Pharmacokinetics	Peak oral absorption occurs at 2–3 hours after the drug dose. Peak concentrations of 2–7 mcg/ml are expected after an oral dose of 500 mg in the nonfasting adult. Because of high intracellular concentrations, tissue levels are higher than in the serum.
Oral absorption	The drug is rapidly absorbed after oral administration and is about 50% bioavailable. It can be given without regard to food. Food slightly delays the peak serum level but also slightly increases the peak concentration achieved.
CSF penetration	There is no information available about CNS penetration
Special circumstances	Pregnancy/Breastfeeding: Pregnancy category C and generally should not be used in pregnancy unless no other alternative is available. It is not known if the drug is excreted in human breast milk. Use in renal disease: The interval between doses should be increased in severe renal disease. See Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i> . Use in hepatic disease: No adjustment is necessary.
Adverse reactions	Diarrhea, nausea, abnormal taste, dyspepsia, abdominal pain/discomfort, headache. Rare allergic skin reactions, liver toxicity, QT prolongation, <i>C.diff</i> colitis, hearing loss

CLARITHROMYCIN (CLR) [2 of 2]

Contraindications	Patients with known hypersensitivity to macrolide antibiotics. Should not be given with the any of the following drugs: Cisapride, pimozone, astemizole, terfenadine, and ergotamine or dihydroergotamine.
Monitoring	No routine laboratory monitoring is indicated.
2012 wholesale cost 30-day supply, 60-kg person	\$16 (outpatient public health pricing) \$271 (community hospital)
Patient instructions	This medication may be taken with or without food. Be sure to tell your doctor what other medications you are taking. Do not take cisapride, pimozone, astemizole, terfenadine, and ergotamine or dihydroergotamine when taking clarithromycin. Stop the medication and call your doctor immediately if you develop severe diarrhea.

CLOFAZIMINE (CFZ) [1 of 2]

Drug class	Iminophenazine
Trade name	Lamprene
Activity against TB	<i>In vitro</i> activity against <i>M. tuberculosis</i> without much <i>in vivo</i> data. Generally reserved for cases with few other options.
Cross-resistance	Bedaquiline. Cross-resistance has been reported in both directions through efflux-based resistance.
Dose (all once daily)	<p>Adults: 100 to 200 mg daily (oral) have been used. A regimen of 200 mg daily for 2 months, followed by 100 mg daily has been used.</p> <p>Children: Limited data, but doses of 1 mg/kg/day have been given.</p> <p>Renal failure/dialysis: No adjustment required.</p>
Route of administration	Oral; not available parenterally.
Preparation	50 and 100 mg capsules.
Storage	Room temperature.
Pharmacokinetics	<p>Tissue half-life estimated to be around 70 days.</p> <p>Peak concentrations 2–3 hours after a dose are expected to be 0.5–2.0 mcg/ml.</p> <p>Peak concentrations occur at 4–8 hours when given with food.</p>
Oral absorption	70% absorption after an oral dose.
CSF penetration	Limited data are available regarding CNS penetration.
Special circumstances	<p>Use in pregnancy/breastfeeding: Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths). Avoided with breastfeeding due to pigmentation of the infant.</p> <p>Use in renal disease: No dosage adjustment required.</p> <p>Use in hepatic disease: Partially metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency.</p>
Adverse reactions	<p>Pink or red discoloration of skin, conjunctiva, cornea, and body fluids.</p> <p>Gastrointestinal intolerance.</p> <p>Photosensitivity.</p> <p>Other side effects include retinopathy, dry skin, pruritus, rash, ichthyosis, xerosis, and severe abdominal symptoms, bleeding, and bowel obstruction.</p>
Contraindications	Allergy to clofazimine.
Monitoring	Symptomatic monitoring.

CLOFAZIMINE (CFZ) [2 of 2]

2012 wholesale cost

Clofazimine is not commercially available within the United States. Clinicians should contact the FDA's Office of Emergency Operations (866-300-4374 or 301-796-8240) in order to apply for a single patient Investigational New Drug (IND). The drug is made available on a case-by-case basis without charge.

Patient instructions

Take with food to avoid stomach upset and improve absorption.

This medicine may discolor your skin and body secretions pink, red, or brownish-black. This should go away after stopping the medicine, but may take a long time. Avoid the sun and use strong sunscreens.

Call your doctor right away if you have:

- Bloody or black stools or diarrhea
- Yellowing of your skin or eyes
- Severe nausea, vomiting, abdominal pain, cramps, or burning
- Depression or thoughts of hurting yourself

CYCLOSERINE (CS) [1 of 2]

Drug class	Analog of D-alanine
Trade name	Seromycin
Activity against TB	Bacteriostatic; inhibits cell wall synthesis.
Cross-resistance	None reported
Dose	<p>Adults: 10–15 mg/kg/day usually; 250 mg PO twice a day or 500 mg PO in a single dose; can increase to 250 mg PO 3 times a day or 250 mg QAM and 500 mg PO QHS if peak concentrations are kept below 35 mcg/ml. Some patients may require only alternate day 250 mg and 500 mg dosing to achieve desired blood levels.</p> <p>Children: 10–20 mg/kg/day divided every 12 hours (daily maximum 1 gram).</p> <p>Vitamin B6: Although supporting data are not extensive, MDR-TB experts recommend that all patients should receive vitamin B6 while taking cycloserine. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight.</p> <p>Renal failure/dialysis: 250 mg once daily or 500 mg 3 times per week; monitor drug concentrations to keep peak concentrations < 35 mcg/ml. See Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p>
Route of administration	Oral; not available parenterally.
Preparation	250 mg capsule.
Storage	Room temperature in airtight containers.
Pharmacokinetics	<p>Peak oral absorption usually occurs by 2 hours (may be up to 4 hours).</p> <p>Peak concentration should be drawn at 2 hours; if delayed absorption is suspected, a concentration at 6 hours will be helpful. A concentration at 10 hours will allow for calculation of the half-life. Allow 3–4 days of drug administration before drawing concentrations due to the long half-life.</p> <p>Peak concentrations are expected to be between 20 and 35 mcg/ml. CNS toxicity is associated with concentrations over 35 mcg/ml, but may occur even at lower concentrations. Some MDR-TB clinicians prefer to keep the concentration below 30 mcg/ml.</p>
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
CSF penetration	Concentrations approach those in serum.
Special circumstances	<p>Use in pregnancy/breastfeeding: Not well studied, but no teratogenicity documented. Use if there are not better choices. Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed).</p> <p>Use in renal disease: Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see above). Use with caution.</p> <p>Use in hepatic disease: Not associated with hepatotoxicity.</p>

CYCLOSERINE (CS) [2 of 2]

Adverse reactions	CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis, and suicidal ideation, <i>usually</i> occur at peak concentrations > 35 mcg/ml, but may be seen in the normal therapeutic range. Other side effects include peripheral neuropathy and skin changes. Skin problems include lichenoid eruptions and Stevens-Johnson syndrome.
Contraindications	Significant CNS disease , including seizure disorder, psychotic disease, or alcohol abuse.
Monitoring	Peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept below 35 mcg/ml. Baseline and monthly monitoring for depression using a tool such as the Beck Depression Index should be done.
2012 wholesale cost 30-day supply, 60-kg person	\$435 (outpatient public health pricing) \$810 (community hospital)
Patient instructions	<p>Best taken on an empty stomach, with juice or antacids. If food is taken, avoid a large fatty meal. Avoid alcohol.</p> <p>You must also take a high-dose vitamin B6 supplement while on this drug.</p> <p>Call your doctor right away if you have:</p> <ul style="list-style-type: none"> • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting yourself • Anxiety, confusion, or loss of memory • Personality changes, such as aggressive behavior • Rash or hives • Headache

DELAMANID (DLM) [1 of 2]

Drug class	Nitroimidazo-oxazole derivative
Trade name	Delyba (in Europe)
Activity against TB	Bactericidal; has strong anti-TB activity. Inhibits mycolic acid biosynthesis.
Cross-resistance	Cross-resistance with investigational drug PA-824, also a Nitroimidazole
Dose	<p>Adults: 100 mg twice daily with food for 24 weeks. Administration for more than 6 consecutive months has not been studied.</p> <p>Children: The safety and efficacy of delamanid in children under 18 years has not been published. Based strictly on weight, converting from the adult doses in a 70 kg patient, estimated pediatric doses would be 1.5 mg/kg twice daily for 24 weeks. However, these doses are not supported by clinical experience. Studies are ongoing, testing delamanid at 50 mg BID for ages 6-11, and 100 mg BID for ages 12-17.</p> <p>Renal failure/dialysis: No dose adjustment needed for mild to moderate renal insufficiency but there are no data regarding use in patients with severe renal impairment. Therefore, delamanid is not recommended for patients with severe renal impairment.</p>
Route of administration	Oral.
Preparation	50 mg film coated tablets.
Storage	Store at room temperature and in original package in order to protect from moisture.
Pharmacokinetics	<p>Time of peak oral absorption (T_{max}) occurs approximately 4 hours post dose. Administration with a standard meal increases bioavailability about 3-fold, therefore drug should be taken with food. The drug is highly protein-bound, and displays a large volume of distribution.</p> <p>Peak concentrations (C_{max}) at steady state (approximately 14 days of administration) were 369 and 361 ng/ml after the first and second dose, respectively (0.37 and 0.36 mcg/ml).</p>
Oral absorption	25- 47% of the delamanid dose is absorbed following oral administration with food.
Metabolism	The drug is predominantly metabolized in plasma by albumin. Minimal metabolism of delamanid also occurs in human liver microsomes by cytochrome P450 (CYP) 3A4.
CSF penetration	No data are available. Also, there are no data on the treatment of extrapulmonary TB (e.g., central nervous system, bone) with delamanid.

DELAMANID (DLM) [2 of 2]

<p>Special circumstances</p>	<p>Use in pregnancy/breastfeeding: Delamanid may cause harm to a fetus. It is usually not recommended for use during pregnancy. It is not known if delamanid passes into breast milk in humans. Breastfeeding is not recommended during treatment with delamanid.</p> <p>Use in renal disease: No dose adjustment needed for mild to moderate renal insufficiency, but delamanid is not recommended for patients with severe renal impairment.</p> <p>Use in hepatic disease: No dose adjustment is necessary for delamanid in patients with mild hepatic impairment, but it is not recommended in patients with moderate to severe hepatic impairment. Delamanid is contraindicated in patients with serum albumin levels <2.8 g/ml.</p> <p>Use in cardiac disease: Patients with various cardiac risk factors, including QTc interval prolongation, should not receive delamanid unless the potential benefits of treatment are expected to outweigh the possible risks. For all patients, an ECG is recommended prior to starting delamanid, and then monthly throughout treatment. Patients with serum albumin levels <3.4 g/ml (but at least 2.8 g/ml), or with cardiac risk factors, should receive more frequent ECG monitoring. Serum electrolytes should be checked and corrected as needed.</p>
<p>Adverse reactions</p>	<p>The most frequent adverse drug reactions noted in controlled trials using delamanid with background regimens were nausea, vomiting, dizziness, insomnia, and upper abdominal pain. QTc prolongation occurred in about 10% of patients receiving 100 mg twice daily. However, no episodes were accompanied by clinical symptoms such as arrhythmias or syncope.</p>
<p>Contraindications</p>	<p>Hypersensitivity to delamanid</p> <p>Serum albumin < 2.8 g/ml because of an increased risk of QTc prolongation</p> <p>Taking other medications that are strong inducers of CYP3A (e.g. carbamazepine, rifamycins)</p>
<p>Monitoring</p>	<p>ECG at baseline and monthly during treatment. Baseline electrolytes, repeat if QTc prolongation occurs.</p>
<p>2012 wholesale cost 24-week supply, 60-kg person</p>	<p>Not available (outpatient public health pricing) Not available (community hospital)</p>
<p>Patient instructions</p>	<p>Take medication with food</p> <p>Tell your doctor if you have one of the following conditions:</p> <ul style="list-style-type: none"> • You have low levels of albumin, potassium, magnesium or calcium in the blood • You have been told that you have heart problems or have a history of heart attack • If you have a condition called congenital long QT syndrome or problems with heart rhythm • You have liver or kidney disease • You have HIV <p>Tell your doctor if you are pregnant or planning on pregnancy.</p>

ETHAMBUTOL (EMB) [1 of 2]

Drug class	Unspecified
Trade name	Myambutol
Activity against TB	Bacteriostatic inhibitor of cell wall synthesis; bactericidal only at the high end of the dosing range. At doses used over long periods of time, ethambutol protects against further development of resistance.
Cross-resistance	None reported
Dose (all once daily)	<p>Adults: 15–25 mg/kg/day. Higher doses should be used only during the initial months of therapy. For prolonged therapy, the dose should be closer to 15 mg/kg/day to avoid toxicity. Intermittent dosing at 50 mg/kg thrice or twice weekly can be used.</p> <p>Children: 15–25 mg/kg/day; doses closer to 15 mg/kg/day should be used if the drug is used for more than 2 months.</p> <p>Renal failure/dialysis: 15–25 mg/kg/dose 3 times weekly (not daily).</p> <p>Obesity: ATS/CDC Guidelines recommend dosing based on estimated lean body weight. Lean Body Weight (men) = $(1.10 \times \text{Weight(kg)}) - 128 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))$ Lean Body Weight (women) = $(1.07 \times \text{Weight(kg)}) - 148 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))$ <i>Serum levels may be monitored.</i></p>
Route of administration	Oral; not available parenterally in the U.S.
Preparation	100 mg tablets; scored 400 mg tablets; coated 100 mg tablets; coated, scored 400 mg tablets.
Storage	Room temperature.
Pharmacokinetics	<p>Peak oral absorption occurs 2–4 hours after the dose. Draw a peak serum concentration 2–3 hours after the dose; a second sample 6 hours post-dose could be obtained if there is concern about late absorption and in order to estimate the serum half-life.</p> <p>Peak concentrations of 2–6 mcg/ml are expected with daily dosing. Intermittent doses of 50 mg/kg can be expected to produce peaks of 4–12 mcg/ml.</p>
Oral absorption	80% bioavailability independent of food.
CSF penetration	Ethambutol penetrates meninges poorly.
Special circumstances	<p>Use in pregnancy/breastfeeding: Safe in pregnancy; can be used while breastfeeding.</p> <p>Use in renal disease: Use with caution—cleared by the kidneys; dose adjustment required for renal failure. Increased risk of toxicity with renal failure. If needed for use in the regimen, consider therapeutic drug monitoring. See Chapter 7, <i>Co-morbidities and Special Situations - Renal Failure</i>.</p> <p>Use in hepatic disease: Safe in liver disease.</p>
Adverse reactions	Retrobulbar neuritis (dose-related—exacerbated during renal failure).

ETHAMBUTOL (EMB) [2 of 2]

Contraindications	Pre-existing optic neuritis; visual changes on ethambutol.
Monitoring	Patients should be counseled to report any changes in vision. Baseline and monthly visual acuity and color discrimination monitoring should be performed (particular attention should be given to individuals on higher doses or with renal impairment).
2012 wholesale cost 30-day supply, 60-kg person	\$20 (outpatient public health pricing) \$140 (community hospital)
Patient instructions	<p>Can be taken with food or on an empty stomach.</p> <p>Call your doctor right away if you have:</p> <ul style="list-style-type: none">• Any problems with your eyes: vision changes, blurring, color blindness, trouble seeing, or eye pain• Swelling of face• Rash, hives, or trouble breathing• Numbness, pain, or tingling in hands or feet• Joint pain• Fever or chills• Nausea, vomiting, poor appetite, or abdominal pain• Headache or dizziness

ETHIONAMIDE (ETA) [1 of 2]

Drug class	Derivative of isonicotinic acid
Trade name	Trecator-SC
Activity against TB	Weakly bactericidal; blocks mycolic acid synthesis.
Cross-resistance	Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide due to mutation in inhA or the promoter region.
Dose	<p>Adults: 15–20 mg/kg/day frequently divided (max dose 1 gram per day); usually 500–750 mg per day in 2 divided doses or a single daily dose. Most patients will experience GI intolerance with ETA doses greater than 1 gram daily.</p> <p>Children: 15–20 mg/kg/day usually divided into 2–3 doses. A single daily dose can sometimes be given at bedtime or with the main meal. Many individuals require gradual ramping up of the dose and treatment for GI upset.</p> <p>Vitamin B6: Although there is little supporting data, most MDR-TB experts recommend that all patients should receive vitamin B6 while taking ethionamide. Adults need 100 mg and children should receive a dose proportionate to their weight.</p> <p>Renal failure/dialysis: No change.</p>
Route of administration	Oral; not available parenterally.
Preparation	Coated 250 mg tablet.
Storage	Store at room temperature.
Pharmacokinetics	<p>Peak oral absorption is usually reached in 2–3 hours, but delayed absorption is common; peak concentrations should be drawn at 2 hours.</p> <p>Peak concentrations are typically 1–5 mcg/ml.</p>
Oral absorption	Erratic absorption, possibly due to GI disturbances associated with the medication.
CSF penetration	Concentrations approach those in serum; one pediatric study evaluating drug concentrations in the CSF suggests that ethionamide should be dosed on the high end of the range for patients with meningitis.
Special circumstances	<p>Use in pregnancy/breastfeeding: Generally avoided during pregnancy due to reports of teratogenicity; little data about use during breastfeeding—an estimated 20% of a usual therapeutic dose is thought to be received (dose the infant with vitamin B6 if breastfed).</p> <p>Use in renal disease: No precautions are required for renal impairment.</p> <p>Use in hepatic disease: Can cause hepatotoxicity similar to that of INH—use with caution in liver disease.</p>

ETHIONAMIDE (ETA) [2 of 2]

<p>Adverse reactions</p>	<p>Gastrointestinal upset and anorexia: Sometimes intolerable (symptoms are moderated by food or taking at bedtime). Premedication with an antiemetic like ondansetron is often helpful. Low dose Ativan 0.5 mg has also been used successfully.</p> <p>Metallic taste.</p> <p>Hepatotoxicity.</p> <p>Endocrine effects: Gynecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism—treat with thyroid replacement.</p> <p>Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side effects may be exaggerated in patients also taking cycloserine.</p>
<p>Contraindications</p>	<p>Sensitivity to ethionamide.</p>
<p>Monitoring</p>	<p>Monitor TSH for evidence of hypothyroidism requiring replacement; therapeutic drug monitoring if malabsorption suspected. Monitor liver function tests.</p>
<p>2012 wholesale cost 30-day supply, 60-kg person</p>	<p>\$177 (outpatient public health pricing) \$378 (community hospital)</p>
<p>Patient instructions</p>	<p>Take this medicine with food.</p> <p>You must also take a high-dose vitamin B6 supplement while on this drug.</p> <p>Call your doctor right away if you have:</p> <ul style="list-style-type: none"> • Any problems with your eyes: eye pain, blurred vision, color blindness, or trouble seeing • Numbness, tingling, or pain in your hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion, or aggression • Yellowing of your skin or eyes • Dark-colored urine • Nausea and vomiting • Dizziness • Swollen breasts (in men)

IMIPENEM/CILASTATIN (IMP/CLN) [1 of 2]

Drug class	Beta-lactam – carbapenem
Trade name	Primaxin
Activity against TB	<i>In vitro</i> activity—very limited clinical experience.
Cross-resistance	Imipenem and Meropenem are both carbapenems and likely to have a moderate probability of cross-resistance
Dose	<p>Adults: 1000 mg IV every 12 hours.</p> <p>Children: Meropenem preferred. See <i>Meropenem</i>.</p> <p>Renal failure/dialysis: Adjustment in dose based on severity of renal failure—for example, 750 mg every 12 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance < 20 ml/min.</p>
Route of administration	IV or IM (total IM doses are not recommended more than 1.5 gram/day and are therefore not very practical for treatment of drug-resistant TB). No oral preparation.
Preparation	Lyophilized powder 1:1 ratio of imipenem and cilastatin. Vials are available 250, 500, 750 mg, or 1 gram.
Storage	Powder should be kept at room temperature; suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
Pharmacokinetics	<p>Peak concentrations occur immediately after IV infusion and 1 hour after IM infusion.</p> <p>Peak concentrations of 35–60 mcg/ml occur after infusion of 1 gram.</p>
Oral absorption	No oral absorption.
CSF penetration	Good CSF penetration, but children with meningitis treated with imipenem had high rates of seizures (meropenem preferred for meningitis and for children).
Special circumstances	<p>Use in pregnancy/breastfeeding: Little information known regarding use in pregnancy; unknown safety during breastfeeding.</p> <p>Use in renal disease: Dose adjustment required (see above); dose after dialysis.</p> <p>Use in hepatic disease: Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented.</p>
Adverse reactions	Diarrhea, nausea, or vomiting. Seizure (noted with CNS infection).
Contraindications	Carbapenem intolerance; meningitis (use meropenem rather than imipenem).
Monitoring	Symptomatic monitoring.
2012 wholesale cost 30-day supply, 60-kg person	\$702 (outpatient public health pricing) \$2,107 (community hospital)

Patient instructions

Make sure your doctor knows if you are also taking ganciclovir or have allergy to penicillins or cephalosporins.

Call your doctor right away if you have:

- Fast or irregular heartbeat
- Seizures
- Severe diarrhea (watery or bloody)
- Skin rash, hives, or itching
- Swelling of the face, throat, or lips
- Wheezing or trouble breathing

ISONIAZID (INH) [1 of 2]

Drug class	Isonicotinic acid hydrazide
Trade name	INH/Isoniazid/Laniazid/Nydrazid
Activity against TB	Bactericidal , especially for rapidly dividing cells. Affects mycolic acid (cell wall) synthesis. Inclusion of INH in the regimen of patients with strain W MDR-TB and other strains with low-level INH resistance were also associated with improved outcomes.
Cross-resistance	Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid due to a mutation in <i>inhA</i> or the promotor region.
Dose (all once daily)	<p>Adults: 5 mg/kg/day (PO or IV) usual adult dose 300 mg daily; high dose INH (900 to 1500 mg twice or thrice weekly) is sometimes used, especially for patients with low-level INH resistance.</p> <p>Children: 10–15 mg/kg/day up to 300 mg (PO or IV); 20–30 mg/kg/dose twice or thrice weekly.</p> <p>Renal failure/dialysis: 300 mg once daily or 900 mg thrice weekly.</p> <p>Vitamin B6 should be used when high-dose INH employed and in patients with diabetes, uremia, HIV infection, alcohol abuse, malnutrition, or peripheral neuropathy. Additionally, pregnant and post-partum women and exclusively breastfeeding infants should receive vitamin B6 while taking INH.</p>
Route of administration	Oral, intravenous, or intramuscular.
Preparation	50 mg, 100 mg, or 300 mg scored or unscored tablets; 50 mg/5 ml oral suspension in sorbitol; solution for injection 100 mg/ml. When given IV, dilute in 25 ml normal saline and infuse as a slow bolus over 5 minutes. Since compatibility information is not available, do not infuse “piggyback” with other drugs through a shared IV line.
Storage	Suspension must be kept at room temperature.
Pharmacokinetics	<p>Peak serum concentrations are achieved at 1–2 hours after the oral dose.</p> <p>Peak concentrations Collect blood for peak serum concentrations 2 hours after a dose (and if desired at 6 hours after a dose in order to calculate half-life).</p> <p>Peak concentration is expected to be 3–5 mcg/ml after daily dose and 9–15 mcg/ml after twice weekly dose.</p>
Oral absorption	Well absorbed orally or intramuscularly; best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal.
CSF penetration	Concentration equivalent to plasma in inflamed meninges. 20% of concentrations in plasma in non-inflamed meninges.

MEDICATION FACT SHEETS

ISONIAZID (INH) [2 of 2]

<p>Special circumstances</p>	<p>Use in pregnancy/breastfeeding: Safe during pregnancy; safe during breastfeeding (both baby and mother should receive pyridoxine supplementation). Up to 20% of the infant therapeutic dose will be passed to the baby in the breast milk.</p> <p>Use in renal disease: No dose adjustment for renal failure, but pyridoxine supplementation should be used.</p> <p>Use in hepatic disease: May exacerbate liver failure. Use with caution.</p> <p>Drug Interactions: Isoniazid is a CYP3A4 inhibitor. INH may increase the concentrations of certain cytochrome P450 enzyme substrates, including phenytoin and carbamazepine.</p>
<p>Adverse reactions</p>	<p>Hepatitis (age-related).</p> <p>Peripheral neuropathy.</p> <p>Hypersensitivity reactions.</p> <p>Other reactions, including optic neuritis, arthralgias, CNS changes, drug-induced lupus, diarrhea, and cramping with liquid product.</p>
<p>Contraindications</p>	<p>Patients with high-level INH resistance who have failed an INH-containing regimen should not receive INH.</p>
<p>Monitoring</p>	<p>Clinical monitoring of all patients on INH is essential. Routine laboratory monitoring is not recommended for patients receiving INH monotherapy. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity. Therapeutic drug monitoring is recommended only for patients suspected of having malabsorption or treatment failure. Monitor concentrations of phenytoin or carbamazepine in patients receiving those drugs (increases phenytoin concentrations and risk of hepatotoxicity with carbamazepine), especially when undergoing INH monotherapy. Rifampin tends to lower concentrations of these drugs and balance effect of INH.</p>
<p>2012 wholesale cost 30-day supply, 60-kg person</p>	<p>\$1 (outpatient public health pricing) \$3 (community hospital)</p>
<p>Patient instructions</p>	<p>Do not take this medication with a large fatty meal. If you have an upset stomach, take the medicine with a snack. If you (or your child) are taking the liquid suspension—do not put it in the refrigerator. Avoid alcohol while taking this medicine. If you need an antacid, don't take it within an hour of this medicine. Make sure your doctor knows if you are also taking medicine for seizures. Let your doctor know if you get flushing, sweating, or headaches when eating certain cheeses or fish. Ask your doctor if you should be taking a vitamin B6 (pyridoxine supplement).</p> <p>Call your doctor right away if you have any of these side effects:</p> <ul style="list-style-type: none"> • Loss of appetite for a few days that is not going away • Tiredness, weakness • Moderate stomach pain, nausea, or vomiting • Numbness or tingling of your fingers or toes • Blurred vision, eye pain • Yellow skin or eyes or dark-colored urine

KANAMYCIN (KM) [1 of 2]

Drug class	Aminoglycoside
Trade name	Kantrex
Activity against TB	Bactericidal; has strong anti-TB activity. Cross-resistance with amikacin and some data suggesting cross-resistance with capreomycin; inhibits protein synthesis.
Cross-resistance	Amikacin: high likelihood of cross-resistance because it is associated with the same mutation (<i>rrs</i>). However, there are some kanamycin mutations (<i>eis</i>) that do not cause amikacin resistance. Some data suggests amikacin cross-resistance with capreomycin.
Dose (all once daily)	<p>Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week.</p> <p>15 mg/kg/dose, 2–3 times per week after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations).</p> <p>> 59 yrs of age: Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week.</p> <p>Children: 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 3 days per week after initial period daily.</p> <p>Renal failure/dialysis: 12–15 mg/kg/dose 2–3 times weekly (not daily).</p> <p>Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p>For dosing, use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft</p> <p><i>Concentrations should be followed closely.</i></p>
Route of administration	Intravenous or intramuscular; not absorbed orally.
Preparation	Clear colorless solution stable at room temperature; 250 mg/ml in vials of 500 mg or 1 gram; 1 gram in 3 ml vial; or 75 mg/vial for infants. Can be mixed with D5W or normal saline for intravenous infusion. Adult doses should be mixed in at least 100 ml of fluid, and pediatric doses should be mixed to a concentration of at least 5 mg/ml.
Storage	Store in the refrigerator.
Pharmacokinetics	<p>For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak concentrations are achieved at 1–2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p>Peak concentrations for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p>Peak concentrations of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations should be undetectable after a 24-hour dose.</p>

KANAMYCIN (KM) [2 of 2]

Oral absorption	Not absorbed orally; 40–80% of the dose is absorbed intramuscularly.
CSF penetration	Minimal and variable CSF penetration—slightly better with inflamed meninges.
Special circumstances	<p>Use in pregnancy/breastfeeding: Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding.</p> <p>Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See “Dose – Renal Failure/Dialysis” (previous page). The drug is variably cleared by hemodialysis, see Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p> <p>Use in hepatic disease: Drug concentrations 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 hepato-renal syndrome.</p> <p>Diuretic use: Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</p>
Adverse reactions	<p>Nephrotoxicity: Appears to be more nephrotoxic than streptomycin.</p> <p>Ototoxicity (hearing loss) and vestibular toxicity: Increased with advanced age and prolonged use; appears to occur slightly more commonly with kanamycin than with streptomycin and about the same frequency as amikacin. Kanamycin seems to have slightly less vestibular toxicity.</p>
Contraindications	Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy); hypersensitivity to aminoglycosides ; caution with renal, vestibular, or auditory impairment; patients with intestinal obstructions.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
2012 wholesale cost 30-day supply, 60-kg person	<p>\$153 (outpatient public health pricing) \$362 (community hospital)</p> <p>Not currently available in the U.S.</p>
Patient instructions	<p>Call your doctor right away if you have:</p> <ul style="list-style-type: none"> • Problems with hearing, dizziness, or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at your IV site • Muscle twitching or weakness

LEVOFLOXACIN (LFX) [1 of 2]

Drug class	Fluoroquinolone (FQN)
Trade name	Levaquin
Activity against TB	Bactericidal; has strong anti-TB activity. Cross-resistance with other fluoroquinolones, but data suggests greater activity than ciprofloxacin or ofloxacin. Inhibits DNA gyrase.
Cross-resistance	In general, there is a complete class effect cross-resistance among fluoroquinolones <i>in vitro</i> . However, data suggest that moxifloxacin may continue to demonstrate some activity despite <i>in vitro</i> resistance to ofloxacin
Dose (all once daily)	<p>Adults: For treatment of TB disease: 500–1000 mg/day (PO or IV). Usually at least 750 mg/day is used and the dose can be increased to 1000 mg if tolerated. For contacts to MDR-TB: 500 mg/day if ≤ 45.5 kg (100 lbs); 750 mg/day if > 45.5 kg (100 lbs).</p> <p>Children: 15-20 mg/kg/day once daily or divided BID for younger children (PO or IV)</p> <p>Renal failure/dialysis: 750–1000 mg/dose 3 times weekly (not daily) for creatinine clearance < 30 ml/min.</p>
Route of administration	Oral or intravenous.
Preparation	Coated tablets (250 mg, 500 mg, 750 mg); solution for injection 25 mg/ml; 250 mg in 50 ml container; 500 mg in 100 ml container; 750 mg in 150 ml container. Oral suspension is 25 mg/ml.
Storage	Oral forms, undiluted solution, and pre-mixed solutions are stored at room temperature. Once diluted, the solution can be kept at room temperature for 3 days, in the refrigerator for 2 weeks, or frozen for 6 months.
Pharmacokinetics	<p>Peak oral absorption occurs at 1–2 hours.</p> <p>Peak concentrations should be drawn at 2 hours after the dose. A second level drawn at 6 hours post dose can distinguish between delayed absorption and malabsorption.</p> <p>Peak concentrations of 8–12 mcg/ml are expected.</p>
Oral absorption	Excellent oral absorption. Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Concentrations are 65% of that in the serum.
Special circumstances	<p>Use in pregnancy/breastfeeding: Fluoroquinolones are generally avoided in pregnancy and breastfeeding due to observation of arthropathy in puppy models. However, there are a few case reports of fluoroquinolones being used safely in pregnancy.</p> <p>Use in renal disease: Dosage adjustment is recommended if creatinine clearance is < 50 ml/min. The drug is not cleared by hemodialysis; supplemental doses after dialysis are not necessary.</p> <p>Use in hepatic disease: Drug concentrations not affected by hepatic disease. Presumed to be safe in severe liver disease.</p>

LEVOFLOXACIN (LFX) [2 of 2]

Adverse reactions	Nausea and bloating. Headache, dizziness, insomnia, or tremulousness. Rare tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation, hypoglycemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication)
Monitoring	Side effect monitoring, but no specific laboratory monitoring required.
2012 wholesale cost 30-day supply, 60-kg person	\$6 (outpatient public health pricing) \$592 (community hospital)
Patient instructions	Avoid caffeinated foods and beverages while taking this medicine; you can take levofloxacin with food. Drink plenty of beverages. Do not take milk-based products, antacids (especially aluminum-containing), mineral supplements such as iron or magnesium, or multivitamins within 2 hours of this medication. This medicine may cause sun sensitivity; use sunscreens. Do not undertake new strenuous activities. Call your doctor and stop the medicine right away if you have: <ul style="list-style-type: none">• Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain• Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest• Diarrhea• Yellow skin or eyes• Anxiety, confusion, or dizziness

LINEZOLID (LZD) [1 of 2]

Drug class	Oxazolidinones
Trade name	Zyvox
Activity against TB	Has <i>in vitro</i> bactericidal activity—increasing clinical experience; inhibits protein synthesis.
Cross-resistance	None reported
Dose	<p>Adults: 600 mg once daily.</p> <p>Children: 10 mg/kg/dose every 12 hours.</p> <p>Vitamin B6: All patients should receive vitamin B6 while receiving linezolid.</p> <p>Renal failure/dialysis: No dose adjustment required.</p>
Route of administration	Oral or intravenous.
Preparation	Coated tablets: 400 and 600 mg; intravenous solution: 2 mg/ml: 100, 200, or 300 mg bags. Oral powder for suspension: 100 mg/5 ml 240 ml bottle.
Storage	Store tablet at room temperature. Reconstituted oral suspension may be stored at room temperature for 21 days. Parenteral preparation should be stored at room temperature (protect from light and do not freeze).
Pharmacokinetics	<p>Intravenous doses are administered over 30–120 minutes.</p> <p>Peak concentrations are achieved 1–1.5 hours after an oral dose and ½ hour after an IV dose.</p> <p>Peak concentrations should be drawn 2 hours after an oral dose or after the end of an IV infusion. A 6-hour post dose concentration can be used to calculate half-life.</p> <p>Peak concentrations are expected to be 12–24 mcg/ml.</p>
Oral absorption	Nearly complete oral absorption.
CSF penetration	CSF concentrations are about 1/3 of those in serum in animal models, and linezolid has been used to treat meningitis in humans.
Special circumstances	<p>Use in pregnancy/breastfeeding: Not recommended during pregnancy or breastfeeding due to limited data.</p> <p>Use in renal disease: No dose adjustment is recommended, but metabolites may accumulate.</p> <p>Use in hepatic disease: Rarely associated with increased transaminases.</p>
Adverse reactions	<p>Myelosuppression.</p> <p>Diarrhea and nausea.</p> <p>Optic and peripheral neuropathy – may be irreversible.</p>

LINEZOLID (LZD) [2 of 2]

Contraindications	<p>Hypersensitivity to oxazolidinones.</p> <p>Symptoms of neuropathy (pain, numbness, tingling or weakness in the extremities).</p> <p>Drug Interactions: Linezolid should generally not be administered to patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs) due to the potential for serious CNS reactions, such as serotonin syndrome. Since MAO type A deaminates serotonin, and SSRIs potentiate the action of serotonin by inhibiting its neuronal reuptake, administration of linezolid concurrently with an SSRI can lead to serious reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions.</p>
Monitoring	Monitor for peripheral neuropathy and optic neuritis. Monitor CBC weekly during the initial period, then monthly, and then as needed based on symptoms; there is little clinical experience with prolonged use.
2012 wholesale cost 30-day supply, 60-kg person	\$1,064 (outpatient public health pricing) \$3,724 (community hospital)
Patient instructions	<p>This medicine may be taken with or without food. Try taking it with food if it bothers your stomach. Avoid food and drinks that contain tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, tap beers, and red wines. Make sure your doctor knows if you're taking medicines for colds, congestion, or depression.</p> <p>Call your doctor right away if you have any of these side effects:</p> <ul style="list-style-type: none">• Pain, numbness, tingling or weakness in the extremities• Black, tarry stools or severe diarrhea• Unusual bleeding or bruising• Unusual tiredness or weakness• Headache, nausea, or vomiting• Changes in vision

MEROPENEM (MPM) [1 of 2]

Drug class	Beta-lactam – carbapenem
Trade name	Merrem I.V.
Activity against TB	<i>In vitro</i> activity—very limited clinical experience.
Cross-resistance	Meropenem and imipenem are both carbapenems and likely to have a moderate probability of cross-resistance.
Dose	<p>Adults: Not established. Only published study used 2000 mg IV every 8–12 hours. Based on pharmacokinetic data 1000 mg every 12 hours may be sufficient. Must be given with clavulanate (available as amoxicillin / clavulanate) 125 mg every 8–12 hours.</p> <p>Children: Not established for TB.</p> <p>For other bacterial infections: 20 mg/kg/dose and 40 mg/kg/dose for meningitis or particularly severe infections are used IV every 8 hours up to 2 gram per dose.</p> <p>Renal failure/dialysis: Adjustment in dose and interval based on severity of renal failure and body weight—for example, 750 mg every 12 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance < 20 ml/min.</p>
Route of administration	IV only; no oral preparation.
Preparation	Crystalline powder. Product is available in 500 mg, or 1 gram vials.
Storage	Powder should be kept at room temperature; suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
Pharmacokinetics	At the end of a 30-minute infusion, peak concentration after a 1 gram dose should be 39–58 mcg/ml. The elimination half-life is approximately 1 hour in patients with normal renal function.
Oral absorption	No oral absorption.
CSF penetration	Adequate CSF penetration
Special circumstances	<p>Use in pregnancy/breastfeeding: Little information known regarding use in pregnancy; unknown safety during breastfeeding.</p> <p>Use in renal disease: Dose adjustment required (see above); dose after dialysis.</p> <p>Use in hepatic disease: Liver disease does not alter the pharmacodynamics of meropenem</p>
Adverse reactions	<p>Diarrhea, nausea, or vomiting.</p> <p>Seizure (noted with CNS infection), but rare compared to imipenem. Rarely elevated LFTs, hematologic toxicity, hypersensitivity</p>
Contraindications	Carbapenem intolerance
Monitoring	Symptomatic monitoring.

MEROPENEM (MPM) [2 of 2]

2012 wholesale cost
30-day supply, 60-kg person

\$674 (outpatient public health pricing)
\$1,109 (community hospital)

Patient instructions

Make sure your doctor knows if you are also taking valproic acid or have allergy to penicillins or cephalosporins.

Call your doctor right away if you have:

- Severe diarrhea (watery or bloody)
- Skin rash, hives, or itching
- Swelling in the face, throat, or lips
- Wheezing or trouble breathing

MOXIFLOXACIN (MFX) [1 of 2]

Drug class	Fluoroquinolone (FQN)
Trade name	Avelox
Activity against TB	Bactericidal; inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on <i>in vitro</i> data.
Cross-resistance	In general, there is a complete class effect cross-resistance among fluoroquinolones <i>in vitro</i> . However, data suggest that moxifloxacin may continue to demonstrate some activity despite <i>in vitro</i> resistance to ofloxacin.
Dose (all once daily)	Adults: 400 mg daily (PO or IV). Children: No established dose. Renal failure/dialysis: No dose adjustment required.
Route of administration	Oral or IV.
Preparation	Tablets (400 mg); aqueous solution (400 mg/250 ml) for IV injection.
Storage	Store oral and IV products at room temperature (do not refrigerate).
Pharmacokinetics	Peak absorption after an oral dose is noted in 1–3 hours. Peak concentrations should be drawn at 2 hours. A 6-hour concentration can be drawn to calculate half-life. Peak concentrations are expected to be 3-5 mcg/ml. Collecting samples at 2 and 6 hours after an oral dose can distinguish between delayed absorption and malabsorption.
Oral absorption	Good oral absorption (90% bioavailable). Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Good penetration in animal model studies.
Special circumstances	Use in pregnancy/breastfeeding: Fluoroquinolones are generally avoided in pregnancy and breastfeeding due to observation of arthropathy in puppy models. However, there are a few case reports of fluoroquinolones being used safely in pregnancy. Use in renal disease: Excretion unchanged in the face of renal failure; no data on effect of dialysis. Use in hepatic disease: Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease.
Adverse reactions	Nausea and diarrhea. Headache and dizziness. Rare tendon rupture; arthralgias. Rare hepatotoxicity. QTc prolongation, hypo/hyperglycemia.

MOXIFLOXACIN (MFX) [2 of 2]

Contraindications	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication).
Monitoring	Symptomatic monitoring.
2012 wholesale cost 30-day supply, 60-kg person	\$80 (outpatient public health pricing) \$684 (community hospital)
Patient instructions	<p>Keep moxifloxacin at room temperature. Moxifloxacin can be taken with food, but do not take milk-based products, antacids (especially aluminum-coating), vitamin supplements, or sucralfate within 2 hours of this medication. Do not undertake new strenuous activities.</p> <p>Call your doctor and stop the medicine right away if you have:</p> <ul style="list-style-type: none">• Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain• Rashes, hives, bruising or blistering, trouble breathing, or tightness in your chest• Diarrhea• Yellow skin or eyes• Anxiety, confusion, or dizziness

PARA-AMINOSALICYLATE (PAS) [1 of 2]

Drug class	Salicylic acid – anti-folate
Trade name	PASER
Activity against TB	Bacteriostatic.
Cross-resistance	None reported.
Dose	<p>Adults: 8–12 grams per day divided 2–3 times per day. Some experts use 6 grams daily.</p> <p>Children: 200–300 mg/kg/day divided 2–4 times per day.</p> <p>Renal failure/dialysis: No change.</p>
Route of administration	Oral; should be given sprinkled on or stirred into yogurt or similar food. Do not chew the granules; they should be swallowed whole. Not available parenterally in the U.S.
Preparation	4 grams per packet.
Storage	Packets should be kept in the refrigerator or freezer.
Pharmacokinetics	<p>Delayed peak concentration with the PASER formulation (the only product available in the United States) due to its enteric coating and sustained release (1–6 hours).</p> <p>Peak concentrations should be collected at 6 hours.</p> <p>Peak concentrations are expected to be 20–60 mcg/ml.</p>
Oral absorption	Incomplete absorption—sometimes requires increased doses to achieve therapeutic concentrations.
CSF penetration	Poorly penetrates the meninges (somewhat better with inflammation).
Special circumstances	<p>Use in pregnancy/breastfeeding: Not studied, but no teratogenicity known. There is little data regarding use during breastfeeding. In one patient, the milk concentration was 1 mcg/ml compared to a serum concentration of 70 mcg/ml.</p> <p>Use in renal disease: Inactive metabolite is cleared by the kidneys.</p> <p>The package insert says to avoid with severe renal failure. Other authorities believe it can be used with caution (no toxicity of metabolite known).</p> <p>Use in hepatic disease: Use with caution; 0.5% incidence of hepatotoxicity.</p>
Adverse reactions	<p>Gastrointestinal distress (less with the PASER formulation than with older preparations).</p> <p>Rare hepatotoxicity and coagulopathy.</p> <p>Reversible hypothyroidism (increased risk with concomitant use of ethionamide)—treat with thyroid replacement.</p>
Contraindications	Pregnancy (relative)
Monitoring	Monitor TSH, electrolytes, blood counts, and liver function tests.

PARA-AMINOSALICYLATE (PAS) [2 of 2]

2012 wholesale cost
30-day supply, 60-kg person

\$173 (outpatient public health pricing)

Patient instructions

Keep the product in the refrigerator or freezer. Sprinkle granules over applesauce or yogurt or swirl in acidic juices (tomato, grape, grapefruit, cranberry, apple, or orange). Do not chew the granules. Take with food if desired. Do not use the packet if expanded or if the granules are discolored. Gastrointestinal discomfort and diarrhea usually improve over time. The shells of the granules may be seen in the stool—this is normal.

Call your doctor right away if you have any of these side effects:

- Skin rash, severe itching, or hives
- Severe abdominal pain, nausea, or vomiting
- Unusual tiredness or loss of appetite
- Black stools or bleeding

PYRAZINAMIDE (PZA) [1 of 2]

Drug class	Synthetic derivative of nicotinamide
Trade name	Pyrazinamide
Activity against TB	Bactericidal for semi-dormant <i>M. tuberculosis</i> . Mechanism unclear.
Cross-resistance	None reported.
Dose (all once daily)	<p>Adults: 25 mg/kg/day. Intermittent dosing at twice or thrice weekly up to 50 mg/kg can be given.</p> <p>Children: 30–40 mg/kg/dose.</p> <p>Renal failure/dialysis: 25 mg/kg/dose 3 times per week (not daily).</p> <p>Obesity: ATS/CDC Guidelines recommend dosing based on estimated lean body weight.</p> <p>Lean Body Weight (men) = $(1.10 \times \text{Weight(kg)}) - 128 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))$ Lean Body Weight (women) = $(1.07 \times \text{Weight(kg)}) - 148 \times (\text{Weight}^2 / (100 \times \text{Height(m)}^2))$</p>
Route of administration	Oral; not available parenterally.
Preparation	500 mg scored or unscored tablet.
Storage	Store the tablets at room temperature.
Pharmacokinetics	<p>Peak concentration is 1–4 hours after an oral dose.</p> <p>Peak concentrations should be drawn at 2 and 6 hours for therapeutic drug monitoring.</p> <p>Peak concentrations of 20–40 mcg/ml are expected after a daily dose. When giving 50 mg/kg intermittently, 60–80 mcg/ml can be expected. An elevated uric acid is an expected finding in every patient on pyrazinamide. If not present, may indicate patient is not taking the drug or there is malabsorption.</p>
Oral absorption	Well absorbed from the GI tract.
CSF penetration	Concentrations equivalent to serum.
Special circumstances	<p>Use in pregnancy/breastfeeding: In the United States, pyrazinamide is avoided in pregnancy for drug-susceptible disease due to lack of data regarding teratogenicity, but should be used for drug-resistant TB when the isolate is susceptible to pyrazinamide (no known teratogenicity). Can be used while breastfeeding.</p> <p>Use in renal disease: Cleared by the kidneys; dose 3 times a week and after dialysis.</p> <p>Use in hepatic disease: Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. It can be quite severe and worsen off treatment.</p>

PYRAZINAMIDE (PZA) [2 of 2]

Adverse reactions	Gout (hyperuricemia) and arthralgias. Hepatotoxicity. Rash. Photosensitivity. Gastrointestinal upset.
Contraindications	Allergy to pyrazinamide; severe gout.
Monitoring	Monitor transaminases and uric acid.
2012 wholesale cost 30-day supply, 60-kg person	\$35 (outpatient public health pricing) \$106 (community hospital)
Patient instructions	May be taken with or without food; this medicine may cause a rash after sun exposure: limit your sun exposure. Call your doctor right away if you have any of these side effects: <ul style="list-style-type: none">• Skin rash, severe itching, or hives• Pain or swelling in the joints• Yellowing of the skin or eyes or dark urine• Nausea or vomiting• Unusual tiredness or loss of appetite

RIFABUTIN (RFB) [1 of 2]

Drug class	Rifamycin
Trade name	Mycobutin
Activity against TB	Bactericidal; same mechanism of activity as rifampin (inhibits RNA polymerase). Less than 20% of rifampin-resistant strains are susceptible to rifabutin.
Cross-resistance	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains that are resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
Dose (all once daily)	<p>Adults: 5 mg/kg/dose (max dose 300 mg, though doses up to 450 mg are sometimes used). Dose adjustments sometimes required when dosing with interacting drugs.</p> <p>Children: The pediatric dose is not established, but doses of 5–10 mg/kg/day have been used (higher doses have been recommended for children < 1 year of age). Caution should be used in very young children in whom visual changes might not be obvious.</p> <p>Renal failure/dialysis: No dose adjustment in mild renal insufficiency. For creatinine clearance less than 30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity.</p> <p>Concomitant medications: Dosage adjustment may be required, particularly with anti-retroviral therapy use. See http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb. If given with ritonavir or cobistat, begin with 150 mg daily. If given with efavirenz, begin with 600 mg daily.</p>
Route of administration	Oral; not available parenterally.
Preparation	150 mg capsule.
Storage	Capsules should be kept at room temperature.
Pharmacokinetics	<p>Peak concentration is reached 3–4 hours after a dose.</p> <p>Peak serum concentration should be drawn 3 hours after the dose; a second sample 7 hours post-dose is desirable in order to distinguish between delayed absorption and malabsorption.</p> <p>The peak concentration should be between 0.3 and 0.9 mcg/ml. Dose adjustments should be considered for patients with concentrations < 0.3 or > 1.0 mcg/ml (low concentrations predict risk of emergence of drug resistance). Rifabutin concentrates in tissues: in lung tissues, concentrations reach 10–20 times that in serum.</p>
Oral absorption	Well absorbed from the GI tract.
CSF penetration	Penetrates inflamed meninges.

RIFABUTIN (RFB) [2 of 2]

<p>Special circumstances</p>	<p>Use in pregnancy/breastfeeding: Insufficient data in pregnancy. Unknown effects from breastfeeding.</p> <p>Use in renal disease: Used without dose adjustment in mild renal insufficiency. For creatinine clearance less than 30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity.</p> <p>Use in hepatic disease: Use with caution and additional monitoring in liver disease. Dose adjustments necessary for drug interactions—especially HIV drugs. See http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb.</p>
<p>Adverse reactions</p>	<p>Leukopenia (dose dependent); thrombocytopenia.</p> <p>Rashes and skin discoloration (bronzing or pseudojaundice).</p> <p>Anterior uveitis and other eye toxicities.</p> <p>Hepatotoxicity similar to that of rifampin.</p> <p>Drug interactions with many other drugs—but only 40% of that seen with rifampin. Rifabutin concentrations may be affected by other drugs.</p> <p>Arthralgias.</p>
<p>Contraindications</p>	<p>Rifamycin hypersensitivity. Data are lacking on cross-sensitivity to rifabutin in patients with hypersensitivity. If used, use with caution, with careful monitoring of patient for development of hypersensitivity. Should not be used for patients with MDR-TB unless susceptibility to rifabutin documented.</p>
<p>Monitoring</p>	<p>Increased liver function monitoring; monitor drug concentrations of interacting medications; blood counts and vision screening.</p>
<p>2012 wholesale cost 30-day supply, 60-kg person</p>	<p>\$75 (outpatient public health pricing) \$970 (community hospital)</p>
<p>Patient instructions</p>	<p>May be taken with or without food; if it bothers your stomach, try taking it with food. It is normal for your urine, tears, and other secretions to turn a brownish-orange color when taking this medicine. Sometimes skin becomes discolored. Soft contact lenses may become discolored while you are on this medicine. Make sure your doctor knows all the medicines you take, as there are many drugs that interfere with this one. Avoid the use of oral hormone-based birth control methods because rifabutin may decrease their effectiveness.</p> <p>Call your doctor right away if you have any of these side effects:</p> <ul style="list-style-type: none"> • Any eye pain, change in vision, or sensitivity to light • Fever, chills, or sore throat • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness or loss of appetite

RIFAMPIN (RIF) [1 of 2]

Drug class	Rifamycin
Trade name	Rifadin (also known as rifampicin)
Activity against TB	Bactericidal; inhibits protein synthesis; cross-resistance with other rifamycins.
Cross-resistance	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
Dose (all once daily)	<p>Adults: 10 mg/kg/dose (PO or IV). Usual dose 600 mg.</p> <p>Children: 10-30 mg/kg/day based on age. See Chapter 6, <i>Pediatrics</i>, Table 3 footnote, page 162, for details. (Maximum 600 mg/day.)</p> <p>Renal failure/dialysis: No adjustment required.</p> <p>Concomitant medications: Dosage adjustment may be required for concurrent medications, including warfarin. After stopping rifampin, warfarin dosage may require downward adjustment to prevent toxicity. Concurrent treatment with most anti-retroviral drugs is not recommended, as anti-retroviral drug concentrations are substantially reduced. On the other hand, rifampin plasma concentrations are not affected by most other drugs, based on current data. See http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/27/hiv-tb.</p>
Route of administration	Oral or intravenous.
Preparation	150 and 300 mg capsules; lyophilized powder for injection: 600 mg/vial; contents of capsules can be mixed with liquid or semi-soft vehicles. Extemporaneously prepared oral solutions have unproven homogeneity and shelf life. Immediate administration of the dose after mixing capsular contents in a vehicle is ideal.
Storage	Capsules and powder should be kept at room temperature; powder suspended in saline is stable for 24 hours; powder suspended in dextrose solutions is stable for 4 hours.
Pharmacokinetics	<p>Peak time to concentration after an oral dose is 1–4 hours.</p> <p>Peak concentrations should be obtained 2 hours after a dose, and if delayed absorption is considered, a concentration at 6 hours should also be collected.</p> <p>Peak concentrations of 8 to 24 mcg/ml are expected. Dose increase should be strongly considered for low concentrations (but not for delayed absorption), as rifampin exhibits a dose response in treatment of TB.</p>
Oral absorption	Usually rapid absorption, may be delayed or decreased by high-fat meals.
CSF penetration	Rifampin CSF penetration is variable and typically achieves only 10–20% of serum concentrations in CSF (may be better in the face of inflamed meninges), but this may still be an important contribution to the regimen. Some authors recommend increased doses of rifampin in patients with TB meningitis.
Special circumstances	<p>Use in pregnancy/breastfeeding: Recommended for use in pregnancy; can be used while breastfeeding.</p> <p>Use in renal disease: Can be used without dose adjustment.</p> <p>Use in hepatic disease: Use with caution, can be associated with hepatotoxicity.</p>

RIFAMPIN (RIF) [2 of 2]

Adverse reactions	Many drug interactions. Orange staining of body fluids. Rash and pruritus. GI upset, flu-like syndrome (usually only with intermittent administration). Hepatotoxicity. Hematologic abnormalities (thrombocytopenia, hemolytic anemia).
Contraindications	Rifamycin allergy; due to drug interactions , may be contraindicated with concurrent use of certain drugs.
Monitoring	Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
2012 wholesale cost 30-day supply, 60-kg person	\$26 (outpatient public health pricing) \$82 (community hospital)
Patient instructions	<p>Best taken without food; if it bothers your stomach, try taking it with a small amount of food. It is normal for your urine, tears, and other secretions to turn an orange color when taking this medicine. Soft contact lenses may become discolored while you are on this medicine. Make sure your doctor knows all the medicines you take because many drugs can interfere with this one. Avoid the use of oral hormone-based birth control methods because rifampin may decrease their effectiveness.</p> <p>Call your doctor right away if you have any of these side effects:</p> <ul style="list-style-type: none">• Unusual tiredness or loss of appetite• Severe abdominal upset• Fever or chills

RIFAPENTINE (RPT) [1 of 2]

Drug class	Rifamycin
Trade name	Priftin
Activity against TB	Bactericidal; same mechanism of action as rifampin, inhibits RNA polymerase. 100% cross-resistant with rifampin.
Cross-resistance	Cross-resistance among the rifamycin class of drugs is typical. In <20% of strains resistant to rifampin, rifabutin may retain susceptibility <i>in vitro</i> . The clinical significance of this is unknown.
Dose for active tuberculosis disease:	<p>Adults: 600 mg once weekly during the continuation phase of treatment. (Not recommended in the U.S. for use during the initial treatment phase and will no longer be recommended in upcoming ATS/CDC treatment guidelines.) Higher daily doses are being studied, with one study suggesting 1200 mg daily with food.</p> <p>Children: (12 years of age and older), 600 mg once weekly if ≥ 45 kg. 450 mg once weekly if < 45 kg.</p>
Dose for LTBI:	<p>Adults: 900 mg once weekly for 12 doses given with INH 900 mg</p> <p>Children: (12 and older), once weekly dose for 12 weeks based on weight (10.0-14.0 kg = 300 mg; 14.1-25.0 kg = 450 mg; 25.1-32.0 kg = 600 mg; 32.1-49.9 kg = 760 mg; ≥ 50 kg = 900 mg) given with INH 15 mg/kg weekly</p> <p>Renal failure/dialysis: No adjustment required. Only 17% of ingested dose is excreted renally.</p> <p>Concomitant medications: Dosage adjustment may be required for concurrent medications. Concurrent treatment with most anti-retroviral drugs is not recommended, as anti-retroviral drug concentrations are substantially reduced, as they are with rifampin. On the other hand, rifapentine plasma concentrations are not affected by most other drugs, based on current data.</p>
Route of administration	Oral
Preparation	150 mg tablets
Storage	Tablets should be stored at room temperature
Pharmacokinetics	<p>Time to peak concentration after an oral dose is 5–6 hours.</p> <p>Peak concentrations after a 600 mg dose are expected to be 8–30 mcg/ml. The half-life is approximately 13 hours.</p>
Oral absorption	Oral bioavailability is 70%. Peak concentration and AUC are increased if given with a meal.
CSF penetration	No information available

MEDICATION FACT SHEETS

RIFAPENTINE (RPT) [2 of 2]

<p>Special circumstances</p>	<p>Use in pregnancy: Pregnancy category C. Use only if potential benefit outweighs possible risk.</p> <p>Use in renal disease: Insufficient data, but likely to be safe since only minimally excreted by the kidneys.</p> <p>Use in hepatic disease: Pharmacokinetics are very similar to normal volunteers in persons with mild to severe liver impairment.</p> <p>Dose adjustments: Not necessary to adjust rifapentine dosage due to drug interactions – but may be needed for concurrent drugs, as is the case for rifampin.</p>
<p>Adverse reactions</p>	<p>Many drug interactions.</p> <p>Red-orange staining of body fluids</p> <p>Rash and pruritis</p> <p>Hypersensitivity reaction</p> <p>Hepatotoxicity</p> <p>Hematologic abnormalities</p>
<p>Contraindications</p>	<p>History of hypersensitivity to any of the rifamycins (i.e., rifampin or rifabutin)</p>
<p>Monitoring</p>	<p>Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.</p>
<p>2012 wholesale cost 30-day supply, 60-kg person</p>	<p>\$54 (outpatient public health pricing) \$109 (community hospital)</p>
<p>Patient instructions</p>	<p>Rifapentine may produce a reddish coloration of your urine, sweat, sputum, tears, and breast milk – be aware that your contact lenses or dentures may be permanently stained. The reliability of oral or other systemic hormonal contraceptives may be affected; consider using alternative contraceptive measures. If you are prone to nausea, vomiting, or gastrointestinal upset, taking rifapentine with food may be useful.</p> <p>Call your doctor right away if you have any of these side effects:</p> <ul style="list-style-type: none"> • Fever • Loss of appetite • Malaise • Nausea and vomiting • Darkened urine • Yellowish discoloration of the skin and eyes • Pain or swelling of the joints

STREPTOMYCIN (SM) [1 of 2]

Drug class	Aminoglycoside
Trade name	Streptomycin sulfate
Activity against TB	Bactericidal; inhibits protein synthesis; no significant cross-resistance with other aminoglycosides.
Cross-resistance	Rarely may be cross-resistant to kanamycin.
Dose (all once daily)	<p>Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have concentrations monitored). 15 mg/kg/dose, 2–3 times per week after initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations).</p> <p>> 59 yrs of age: Many experienced clinicians prefer to use a lower starting dose of 10 mg/kg (5–7 times per week or 2–3 times per week after initial period). Alternatively, 15 mg/kg/dose 3 times per week.</p> <p>Children: 20–40 mg/kg/day (max 1 gram) 5–7 days per week. 20–40 mg/kg/day (max 1 gram) 3 days per week after initial period daily.</p> <p>Renal failure/dialysis: 12–15 mg/kg/dose 2–3 times weekly (not daily).</p> <p>Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations.</p> <p>For dosing, use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft <i>Concentrations should be followed closely.</i></p>
Route of administration	Intravenous or intramuscular (has been used intrathecally and intraperitoneally). Not absorbed orally.
Preparation	1 gram vial for injection.
Storage	Store in the refrigerator.
Pharmacokinetics	<p>For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children; intramuscular absorption is complete within 4 hours and peak concentrations are achieved at 1–2 hours. Obtaining a drug concentration 90–120 minutes after intravenous infusion allows for complete distribution of drug. An additional concentration collected 4 hours later will allow for a half-life to be calculated and peak to be back-extrapolated.</p> <p>Peak concentrations for a 15 mg/kg dose are between 35 and 45 mcg/ml.</p> <p>Peak concentrations of 65–80 mcg/ml are obtained after a 25 mg/kg dose.</p> <p>Trough concentrations should be < 5 mcg/ml in patients with normal renal function.</p>
Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.
CSF penetration	Variable penetration; appears to penetrate inflamed meninges better.

STREPTOMYCIN (SM) [2 of 2]

<p>Special circumstances</p>	<p>Use in pregnancy/breastfeeding: Avoided in pregnancy due to documented cases of congenital deafness. Can be used while breastfeeding.</p> <p>Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See “Dose – Renal Failure/Dialysis” (previous page). The drug is variably cleared by hemodialysis; see Chapter 7, <i>Co-morbidities and Special Situations – Renal Failure</i>.</p> <p>Use in hepatic disease: Drug concentrations not affected by hepatic disease (expect 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 hepato-renal syndrome.</p> <p>Diuretic use: Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.</p>
<p>Adverse reactions</p>	<p>Nephrotoxicity: Less nephrotoxic than amikacin.</p> <p>Ototoxicity (hearing loss): Increased with advanced age and prolonged use.</p> <p>Vestibular toxicity.</p> <p>Local pain with IM injections.</p> <p>Electrolyte abnormalities, including hypokalemia, hypocalcemia, and hypomagnesemia.</p>
<p>Contraindications</p>	<p>Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy); hypersensitivity to aminoglycosides; caution with renal, vestibular, or auditory impairment.</p>
<p>Monitoring</p>	<p>Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.</p>
<p>2012 wholesale cost 30-day supply, 60-kg person</p>	<p>\$178 (outpatient public health pricing) \$450 (community hospital)</p>
<p>Patient instructions</p>	<p>Store streptomycin in the refrigerator.</p> <p>Call your doctor right away if you have:</p> <ul style="list-style-type: none"> • Problems with hearing, dizziness, or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhea • Swelling, pain, or redness at your IV site • Muscle twitching or weakness

New Anti-TB Drugs in the Pipeline

CLINICAL TRIALS		
PHASE I	PHASE II	PHASE III
TBA-354 Nitroimidazole	Sutezolid (PNU-100480) Oxazolidinone	Bedaquiline (TMC 207) with OBR* for MDR-TB Diarylquinoline
Q203-Novel anti-TB agent Imidazopyridine	SQ109 Ethylenediamine	Delamanid (OPC-67683) with OBR* for MDR-TB Nitro-dihydro-imidazooxazole Submitted for FDA approval
	Rifapentine for drug-susceptible TB Rifamycin	Petromanid – Moxifloxacin – Pyrazinamide New chemical entity
	Bedaquiline - Pretomanid – Pyrazinamide regimen	<i>*Optimized Background Regimen</i>
	Levofloxacin Fluoroquinolone	

For updated information, see <http://www.newtbdrugs.org/pipeline.php>

References

- American Academy of Pediatrics. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Pickering LK, ed. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.
- American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR*. 2003;52 (RR-11):1-77.
- Aronoff GR, Berns JS, Brier ME, et al, eds. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 4th edition. Philadelphia: American College of Physicians; 1999:56.
- Balfour JA, Wiseman LR. Moxifloxacin. *Drugs*. 1999;57(3):363-374.
- Benator C, Bhattacharya M, Bozeman L, et.al. Rifapentine and INH once a week vs Rifampin and INH twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients. *Lancet*. 2002;360:528-534.
- Berning SE, Cherry TA, Iseman MD. Novel treatment of meningitis caused by multidrug-resistant *Mycobacterium tuberculosis* with intrathecal levofloxacin and amikacin: case report. *Clin Infect Dis*. 2001;32(4):643-646.
- Blumer JL. Fluoroquinolone use in children: resistance and safety implications. *Contemp Pediatr*. 2003;20(11):97-113.
- Chambers HF, Turner J, Schechter GF, Kawamura M, Hopewell PC. Imipenem for treatment of tuberculosis in mice and humans. *Antimicrob Agents Chemother*. 2005;49(7):2816-2821.
- Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2012;16(4):447-454.
- Destache CJ, Pakiz CB, Larsen C, Owens H, Dash AK. Cerebrospinal fluid penetration and pharmacokinetics of levofloxacin in an experimental rabbit meningitis model. *J Antimicrob Chemother*. 2001;47:611-615.
- Donald PR, Seifart HI. Cerebrospinal fluid concentrations of ethionamide in children with tuberculous meningitis. *J Pediatr*. 1989;115(3):483-486.
- Gupta R, Gao M, Cirule A, Xiao H, Geiter L. Delamanid for extensively drug-resistant tuberculosis. [correspondence] *N Engl J Med*. 2015; 373:291-292.
- Lessnau KD, Qarah S. Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature. *Chest*. 2003;123(3):953-956.
- Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on cycloserine, ethionamide, para-aminosalicylate, and clofazimine. *Chest*. 1999;116(4):984-990.
- Maus CE, Plikaytis BB, Shinnick TM. Molecular analysis of cross-resistance to capreomycin, kanamycin, amikacin, and viomycin in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 2005; 49(8):3192-3197.
- *Micromedex® Healthcare Series* [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. Accessed mobileMicromedex® 2.0 12/02/12.
- Otsuka Pharmaceutical Development & Commercialization, Inc. Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC-67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy With an Optimized Background Regimen of Anti-tuberculosis Drugs Over a 6-Month Treatment Period. In ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/study/NCT01859923?term=delamanid&rank=1> Accessed September 11, 2015.
- Pea F, Pavan F, Nascimben E, et al. Levofloxacin disposition in cerebrospinal fluid in patients with external ventriculostomy. *Antimicrob Agents Chemother*. 2003;47(10): 3104-3108.
- Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs*. 2002;62(15): 2169-2183.
- Peloquin CA. Using therapeutic drug monitoring to dose the antimycobacterial drugs. *Clin Chest Med*. 1997;18(1):79-87.
- Nitta AT, Milligan D. Management of four pregnant women with multidrug-resistant tuberculosis. *Clin Infect Dis*. 1999;28(6):1298-1304.
- Schaad UB. Pediatric use of quinolones. *Pediatr Infect Dis J*. 1999;18(5):469-470.
- Seaworth BJ. Multidrug-resistant tuberculosis. *Infect Dis Clin North Am*. 2002;16(1):73-105.
- Sterling TR, Villarino E, Borisov AS, et.al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *New Eng J Med*. 2011; 365(23): 2155-2166.

- Veziris N, Truffot C, Mainardi J-L, Jarlier V. Activity of carbapenems combined with clavulanate against murine tuberculosis. *Antimicrob Agents Chemother.* 2011;55(6): 2597-2600.
- Wells C, Gupta R, Hittel N, et al. Long-term mortality assessment of multidrug resistant tuberculosis patients treated with delamanid. *Eur Respir J.* 2015;45:1-3
- Zhu M, Namdar R, Stambaugh JJ, et al. Population pharmacokinetics of ethionamide in patients with tuberculosis. *Tuberculosis (Edinb).* 2002;82(2-3):91-96.
- Zhu M, Starke JR, Burman WJ, et al. Population pharmacokinetic modeling of pyrazinamide in children and adults with tuberculosis. *Pharmacotherapy.* 2002;22(6):686-695.