# A UK based resource to support the monitoring and safe use of anti-tuberculosis drugs and second line treatment of multidrug-resistant tuberculosis

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## Abbreviations

| | |
|---|---|
| BNF | British National Formulary |
| BPM | Beats per minute |
| BTS | British Thoracic Society |
| CNS | Central Nervous System |
| DOT | Directly Observed Therapy |
| ECG | Electrocardiogram |
| FBC | Full blood count |
| FDA | Food and Drug Administration (USA) |
| G6PD | Glucose-6-pyruvate dehydrogenase |
| HIV | Human Immunodeficiency Virus |
| IM | Intra-muscular |
| IV | Intra-venous |
| LFT | Liver function tests |
| MDR-TB | Multidrug-resistant tuberculosis |
| Mg | Magnesium |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| QT/ QTc | QT interval/ corrected QT interval |
| SPC | Summary of product characteristics |
| SST | Serum separating tube |
| TB | Tuberculosis |
| TFT | Thyroid function test |
| U&E | Urea & Electrolytes (including creatinine, urea, potassium and sodium) |
| UK | United Kingdom |
| WHO | World Health Organisation |

## Introduction

This guideline is to aid monitoring for adverse effects during the treatment of MDR-TB. It is not a treatment guide or a guide for monitoring the progress of treatment. For treatment guidance please refer to the WHO treatment guideline and the BTS MDR-TB Clinical Advisory Service. Treatment of MDR-TB should always be undertaken in consultation with local experts as well as published guidance.

Due to the complexity of treatment regimens and comorbidity associated with the disease itself, more frequent monitoring may be needed in individual patients and this should be guided by the clinician in charge of the patient's care. Our recommendations are predominantly based on consensus opinion from TB physicians, pharmacists, nursing staff and specialties including audiology and ophthalmology and drug advisory organisations including the FDA and BNF.

We also appreciate that most patients with MDR-TB are established on treatment whilst an in-patient and may require more frequent blood test monitoring during the initial phase of treatment. We have produced this document to provide advice on the frequency of monitoring which should occur, *at minimum*, in all patients on MDR-TB treatment.

Many side effects cannot easily be measured with routine testing. As such, it is important that all healthcare staff routinely assess patients for symptoms with reference to the potential adverse reactions listed for each drug.

All recommendations below should cover any combination of drugs. Where additional monitoring is required with a specific drug we have noted this and provided a source for further information in the form of individual drug monographs.

Therapeutic drug level monitoring advice is available in individual drug monographs.

**Links**

British Thoracic Society MDR-TB Clinical Advisory Service:
https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/
WHO guidance on the treatment of MDR-TB:
https://www.who.int/publications/i/item/9789240007048

## Contents

*NB: WHO have issued a rapid guidance in August 2018 with substantive changes to all treatment groups in the last 2016 MDR guidance* ***advising that capreomycin and kanamycin should not be used in MDR TB. Amikacin is still within their guidance but this is now downgraded to a group C medication with Bedaquiline now being upgraded to a group A drug****. However given that these new guidelines need to be agreed to be implemented locally and nationally, individual cases should still be managed with expert MDR advice and also in conjunction with the BTS MDR Clinical Advice Service review.*

**Baseline and generic tests for adverse effects monitoring in patients being treated for MDR-TB**

| BASELINE TESTS | |
|---|---|
| **Blood Tests** | Renal function and electrolytes (U&Es), liver function tests (LFTs), bone profile, magnesium (Mg), thyroid function tests (TFTs), uric acid |
| | Full blood count (FBC), clotting |
| | HIV, Hepatitis B, Hepatitis C |
| | G6PD deficiency screen |
| **Other Tests** | ECG |
| | Visual Acuity and Colour Vision |
| | Audiometry |
| | Nutritional Assessment |

| ONGOING MONITORING RECOMMENDATIONS | | |
|---|---|---|
| **FBC** | Monthly until 6 months. Consider reducing frequency after 6 months if stable and no changes to medication. If using Linezolid please see individual drug monograph for FBC frequency recommendations. | Many drugs can effect blood cell counts but those on Linezolid at particular risk. |
| **Clotting** | Baseline and repeat if indicated, particularly if deranged LFTs. | |
| **U&Es** | All MDR patients should be on an aminoglycoside therefore:<br>Month 1 = twice weekly<br>Month 2 = weekly<br>Month 3 onwards: fortnightly<br>Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable.<br>Consider increasing frequency of monitoring if evidence of renal impairment. | Aminoglycosides are associated with nephrotoxicity.<br>Monitoring electrolytes also important to consider in those taking drugs that prolong QTc. |
| **LFTs** | Weekly for the first month or until regimen is established, whichever is longest. Then to continue monthly throughout treatment. Consider reducing frequency after 6 months if LFTs stable and no pre-existing liver disease or changes to medication. | Several drugs cause hepatotoxicity. |
| **Calcium** | Monthly until 6 months. Consider reducing frequency after 6 months if stable and no changes to medication. | Aminoglycosides can cause hypocalcaemia. |
| **TFTs** | Monthly if patient on prothionamide and PAS combination therapy. If on only prothionamide or PAS, check TFTs 3 monthly. | |
| **Magnesium** | Monthly until 6 months. Consider reducing frequency after 6 months if stable and no changes to medication. | Aminoglycosides can cause hypomagnesaemia. |

**Baseline and generic tests for adverse effects monitoring in patients being treated for MDR-TB**

| | | |
|---|---|---|
| | | Monitoring electrolytes also important to consider in those taking drugs that prolong QTc. |
| **Lactate** | Consider measuring lactate in anyone with symptoms of lactic acidosis: nausea, vomiting, weightloss, hyperventilation,and tachypnea. | Increased risk in those on Linezolid longer than 6 weeks. |
| **ECG**<br>(For patients prescribed macrolides, fluoroquinolones, clofazamine, bedaquiline or delaminid) | Baseline, at 2 weeks, then 3 monthly (1 monthly if on bedaquiline or<br>delamanid) throughout treatment.<br>Repeat if symptomatic or after the addition of any new medication which is known to prolong QT.<br>Be particularly cautious when prescribing more than one drug which might prolong QTc such as ondansetron, anti-depressants, anti-psychotics etc.<br>If on more than one drug which prolongs QTc we recommend monthly monitoring once stable.<br>Increase monitoring to 2 weekly if QTc outside the normal range (>470 in women, >450 in men).<br>Stop offending medication if QTc greater than 500 and refer to EP cardiologist. | Particular caution should be taken for those on more than one drug that prolongs QTc and consideration of concomitant non-TB drug treatments that may also prolong QTc such as anti-emetics.<br>For more information see: www.qtdrugs.org |
| **Visual acuity & Colour Vision** | Patients should be encouraged to report any changes in vision throughout treatment. Snellen & Ishihara plate testing should be performed 6 monthly or sooner if symptoms noted.<br>Refer for formal assessment with ophthalmology if baseline abnormality or changes noted during treatment. | Please see individual monographs if taking ethambutol or linezolid when more frequent monitoring is recommended. |
| **Audiometry** | Monthly until completion of treatment and a final test 2 months after treatment completion. Repeat sooner if symptoms of ototoxicity such as change in hearing, tinnitus, vertigo or balance disturbance. | Aminoglycosides cause ototoxicity. |

# DRUG MONOGRAPHS

# AMIKACIN

*Please note amikacin is not licensed for the treatment of tuberculosis in the UK.*

## DOSAGE

For intramuscular or intravenous administration only. (Intravenous route is preferred, as the volume of doses required would necessitate two IM injections given as a once daily dose.)

Amikacin is usually given once daily (although for pragmatic reasons there is experience giving it 5 days per week) for an initial period (usually at least two months). In clinical practice the frequency is usually then reduced to three times weekly.

**Single-Dose Regimen** (usually as an intravenous infusion, diluted in 100mL sodium chloride 0.9% or glucose 5% and infused over 30 to 60 minutes):
**Adults: 15mg/kg daily** (usual maximum 1g daily, but can be increased if necessary in large muscular adults). After initial period (usually at least two months): **15mg/kg three times per week**.
**Age >59 years: 10mg/kg daily** (maximum 750mg daily). After initial period: **10mg/kg three times per week**.

**Renal failure: 12-15mg/kg** TWO to THREE times a week. *Please discuss with a pharmacist.*

**Obesity:** It has been suggested that markedly obese patients should have an adjusted dose using ideal body weight plus 40% of the excess weight in markedly obese patients. The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.

- Male ideal body weight (kg) = 50 + (2.3 x height in cm above (152.4/2.54))
- Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above (152.4/2.54))

Adjust dose and/or frequency according to serum amikacin concentration (see below).

**Children: 15-20mg/kg daily** (usual maximum 1g daily). After initial period: **15-30mg/kg three times per week**.
Adjust dose and/or frequency according to serum amikacin concentration (see below).

## PREPARATIONS

**Parenteral:** 100mg/2mL, 500mg/2mL injection.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Ensure therapeutic dose.
- Ensures that accumulation is not occurring in renal impairment.

**Target Level:** <5mg/L (*trough*)
25 – 35mg/L (*peak)*

**Timing of sample:**

- Pre dose.



The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

- Take a level 90 – 120 minutes and 6 hours after the infusion ends. Then plot on semi-logarithmic paper and extrapolate back to time = 0 and use this as the peak level.
- Alternatively, taking a level 60mins after infusion ends may be appropriate as a measure of the peak level, but may underestimate the true peak level.

**Frequency of Levels:**

- Peak serum level in first week, repeat if poor response.
- Trough serum levels weekly for 4 weeks. This can reduce to fortnightly when stable.

**Suggested Actions:**

- **Trough level**: High – extend interval.
- **Peak level**: High – reduce dose; low – increase dose.

## ADVERSE EFFECTS

**COMMON:**
**Nephrotoxicity:** Accumulation if renal impairment.
**Ototoxicity:** Irreversible vestibulo-cochlear nerve damage.
**SERIOUS:**
**Endocrine:** Hypocalcaemia, hypomagnesaemia, and hypokalaemia.
**Neurological:** Neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually dose-related and self-limiting).
**Audiological:** Ototoxicity - auditory > vestibular (higher with prolonged use and older age)
**Renal:** Nephrotoxicity (higher with prolonged use).

## ADVERSE EFFECTS: MONITORING

**Renal**, **auditory** and **vestibular** monitoring is essential
**Renal function**: Month 1 = twice weekly.
Month 2 = weekly.
Month 3 to end of treatment = fortnightly.
Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable.
Consider increasing frequency of monitoring if evidence of renal impairment.

**Loss of hearing** usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances including tinnitus are also signs of **ototoxicity.**

**Genetic testing (R.65 MT-RNR1 155A>G):**

Commented [CT(THNT1]: New - to add this

- Consider genetic testing for mitochondrial mutations, particularly the m.1555A>G mutation prior to starting treatment. MHRA safety review found an increased risk of deafness when using aminoglycosides in patients with mitochondrial mutations.
- Mitochondrial mutations are rare (estimated prevalence is 0.2% in the general population) and the penetrance of the increased ototoxic effect is unknown.

*Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies. If this occurs, Amikacin should be discontinued or dosing reduced in frequency to avoid further hearing loss, although the hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change. Of the current injectable agents, Capreomycin may be less ototoxic.*



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We recommend that patients have baseline audiometry and then monthly reviews until treatment with aminoglycoside ceases. A final audiometry review should be offered 2 months after the final dose.

Routine tests as per generic MDR-TB drug monitoring guidelines.

## INTERACTIONS

Increased risk of **ototoxicity** if given with: loop diuretics
Increased risk of **hypocalcaemia** with bisphosphonates.
Increased risk of **nephrotoxicity** if given with: capreomycin, cephalosporins, ciclosporin, colistimethate sodium, tacrolimus.
*NB: There is no clinical benefit in prescribing amikacin AND capreomycin or kanamycin or streptomycin.*

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To amikacin or other aminoglycosides.
**Myasthenia Gravis:** As amikacin may impair neuromuscular transmission.
**Pregnancy:** Risk of vestibular or auditory nerve damage to foetus if used in second or third trimester.

**Cautions:**
**Obese:** Use ideal weight for height to calculate dose and monitor serum amikacin levels closely.
**Elderly:** Nephrotoxicity and ototoxicity common in the elderly; monitor and reduce dose if necessary.
**Renal Disease:** Use with caution. Reduce the frequency of dosing and monitor serum concentrations.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider for contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
**Sample Type**: Serum.
**Volume Required**: 1-2mL (min 0.1mL).
**Sample Container**: Plain glass or plastic (non SST).
**Container Type**: Any.
**Availability**: NS.
**Turnaround Time**: Telephoned same day if received 9am-3pm Mon-Fri. Written confirmation report will be sent by 1st Class post.



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# BEDAQUILINE

## DOSAGE

**Adults (aged 18 to 64 years):** 400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks. (Maximum duration = 6 months).

**Children:**

| Weight | Age (months) | Dose* |
|---|---|---|
| <3kg | - | Consult with Specialist |
| 3-<7kg | 0-<3 months | 30mg once daily for 14 days, followed by 10mg once daily three times per week* |
| | ≥3 months | 60mg once daily for 14 days, followed by 20mg once daily three times per week* |
| 7-<10kg | 0-<3 months | 30mg once daily for 14 days, followed by 10mg once daily three times per week* |
| | 3-<6 months | 60mg once daily for 14 days, followed by 20mg once daily three times per week* |
| | ≥6 months | 80mg once daily for 14 days, followed by 40mg once daily three times per week* |
| 10-<16kg | 3-<6 months | 60mg once daily for 14 days, followed by 20mg once daily three times per week* |
| | ≥6 months | 120mg once daily for 14 days, followed by 60mg once daily three times per week* |
| 16-<30kg | - | 200mg once daily for 14 days, followed by 100mg once daily three times per week* |
| 30-<46kg | - | 400mg once daily for 14 days, followed by 200mg once daily three times per week* |
| ≥46kg | - | 400mg once daily for 14 days, followed by 200mg once daily three times per week* |

When available, bedaquiline 20mg dispersible tablets should be prioritised for young children over the adult 100mg formulation. Alternatively, Bedaquiline 100mg tablets can be crushed and suspended in water, and have been shown to be bioequivalent to tablets swallowed whole.

*Bedaquiline should be taken with food.*
*Patients should be advised to avoid alcohol whilst on bedaquiline.*

## PREPARATIONS

**Oral:** 100mg tablets, 20mg dispersible tablets

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

- **Report all suspected adverse drug reactions to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme.**

**COMMON:**



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**Arthralgia**
**Chest pain**
**Gastrointestinal:** Nausea.
**Neurological**: Headache.
**Respiratory:** Haemoptysis

**SERIOUS:**
**Cardiovascular:** QTc prolongation (more common in hypokalaemia, proarrhythmic conditions, in combination with other drugs that prolong the QT interval such as clofazimine, fluoroquinolones or macrolides).
**Hepatic**: Increases in LFTs.

## ADVERSE EFFECTS: MONITORING

**ECG:** Baseline, 2 weeks then every month and after the addition of any new medication that is known to prolong QT.

- Discontinue bedaquiline and all other QT prolonging drugs if the patient develops:
  - Clinically significant ventricular arrhythmia
  - A QTc interval of > 500 ms (confirmed by repeat ECG)
- Monitor ECGs frequently to confirm that the QTc interval has returned to baseline.
- If syncope occurs, obtain an ECG to detect QT prolongation.

**LFTs:** at baseline, and repeated monthly.
**U&Es, calcium & magnesium:** at baseline and repeated monthly and if QT prolongation is detected.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTIONS

**Anti-arrhythmics:** Risk of prolonged QT interval (e.g. amiodarone, sotalol, procainamide, dysopyramide and quinidine).
**Antiretrovirals:** Limited data.
**Antidepressants, Tricylic:** Risk of prolonged QT interval**.**
**Antipsychotics (thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole, and pimozide):** Risk of prolonged QT interval**.**
**Azole antifungals (e.g. ketoconazole, voriconazole, itraconazole, fluconazole):** Increased exposure to bedaquiline. Avoid co-administration for more than 14 days.
**Carbamazepine:** Accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
**Chloroquine & hydroxychloroquine:** Risk of prolonged QT interval.
**Clofazimine:** Risk of prolonged QT interval.
**CYP3A4 inducers:** Accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
**CYP3A4 inhibitors:** Reduced metabolism resulting in increased serum concentrations of bedaquiline. Avoid prolonged co-administration for more than 14 days.
**Fluoroquinolones:** Risk of prolonged QT interval.
**Macrolides:** Risk of prolonged QT interval. Avoid co-administration for more than 14 days.
**Phenytoin:** accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.


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**Rifampicin, Rifabutin & Rifapentine:** accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
**Statins:** Avoid co-administration.

*This information is not inclusive of all drug interactions. Please refer to the SPC or BNF for further information, or discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To bedaquiline**.**
**Children aged <18 years:** The safety and effectiveness has not been established in children.

**Cautions:**
**Elderly patients ≥ 65 years:** Lack of data in patients aged 65 and over to determine whether they respond differently from younger patients.
**Pregnancy**: Limited data in humans. Animal data suggests low risk. Consider using if the benefits of treatment outweigh the risks of not treating.
**Breastfeeding:** No data. Expected to be excreted into the breast milk, but high plasma protein binding may reduce the amount excreted. Systemic exposure in breastfed infants may be similar to the breastfeeding mothers. Manufacturer recommends avoiding breastfeeding.
**Extrapulmonary TB** (e.g. meningitis): There are no data on the use of bedaquiline in extra pulmonary TB and consequently it is not currently recommended for the treatment of this.
**Cardiovascular**: Due to the risk of QT prolongation with bedaquiline, ECGs should be monitored closely in patients:

- Taking other QT prolonging drugs (e.g fluoroquinolones, macrolides, clofazimine).
- with a history of Torsade de Pointes, congenital long QT syndrome, hypothyroidism and bradyarrhythmias, or uncompensated heart failure .
- With serum calcium, magnesium, or potassium levels below the lower limits of normal.

**HIV/TB co-infection**: limited or no information on the use of bedaquiline.
**Alcohol or substance use:** Limited or no information on alcohol or substance use in association with bedaquiline however, manufacturer recommends avoiding alcohol whilst taking bedaquiline.
**Liver disease:** Lack of data in severe liver disease. No dose adjustment required in mild to moderate hepatic impairment.
**Renal disease:** Use with caution in patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider for contact details. Turnaround time is usually a few days to a week but this can be reduced by calling ahead and informing the laboratory in advance.



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# CAPREOMYCIN

## DOSAGE

Capreomycin is usually given once daily for an initial period (usually at least two months), then the frequency may be reduced to three times weekly.

**Licensed for intramuscular administration only.** There is experience of using capreomycin as an intravenous infusion. (Diluted in 100 mL of 0.9% Sodium Chloride or glucose 5% and administered over 30 to 60 minutes.)
**Adults: 15mg/kg daily** (usual maximum 1g daily, but can be increased if necessary in large muscular adults). After initial period: **15mg/kg three times per week**.
**Age >59 years: 10mg/kg daily** (maximum 750mg daily). After initial period: **10mg/kg three times per week**.

**Renal failure: 12-15mg/kg** TWO to THREE times a week. *Please discuss with a pharmacist.*

**Obesity:** It has been suggested that markedly obese patients should have an adjusted dose using ideal body weight plus 40% of the excess weight in markedly obese patients. The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.

- Male ideal body weight (kg) = 50 + (2.3 x height in cm above (152.4/2.54))
- Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above (152.4/2.54))

**Children: 15-30mg/kg daily** (usual maximum 1g daily). After initial period: **15-30mg/kg three times per week**.

## PREPARATIONS

**Parenteral:** 1g powder for injection.

## DRUG LEVEL MONITORING

Drug levels cannot currently be performed for capreomycin in the UK.

## ADVERSE EFFECTS

**COMMON:**
**Nephrotoxicity:** Higher risk with prolonged use.
**Ototoxicity:** Auditory > vestibular (Maybe lower risk than with amikacin; higher risk with prolonged use and older age).
**Drug-induced eosinophilia**: Usually subsides with intermittent dosing.
**SERIOUS:**
**Dermatological:** Induration and local pain with IM injection.
**Endocrine:** Hypocalcaemia, hypomagnesaemia, and hypokalaemia.
**Hepatic:** Liver function test abnormalities when used with other anti-TB drugs.
**Neurological:** Neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually with rapid IV infusion).
**Audiological:** Ototoxicity - auditory > vestibular (Maybe less than with amikacin; higher with prolonged use and older age).

**Renal:** Nephrotoxicity (higher with prolonged use).

## ADVERSE EFFECTS: MONITORING

**Renal**, **auditory** and **vestibular** monitoring is essential.

**Renal function**: Month 1 = twice weekly.
Month 2 = weekly.
Month 3 to end of treatment = fortnightly.
Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable.
Consider increasing frequency of monitoring if evidence of renal impairment.

**Loss of hearing** usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances including tinnitus are also signs of **ototoxicity.**

*Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies. If this occurs, Capreomycin should be discontinued or dosing reduced in frequency to avoid further hearing loss, although the hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change.*

We recommend that patients have baseline audiometry and then monthly reviews until treatment with aminoglycoside ceases. A final audiometry review should be offered 2 months after the final dose.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTIONS

Increased risk of **nephrotoxicity** if given with: aminoglycosides, colistimethate sodium.
Increased risk of **ototoxicity** if given with: aminoglycosides.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To capreomycin.
**Pregnancy:** Risk of vestibular or auditory nerve damage to infant if used in second or third trimester.

**Cautions:**
**Renal Disease:** Use with caution. Reduce the frequency of dosing and monitor serum concentrations.
**Obese:** Use ideal weight for height to calculate dose and monitor serum-aminoglycoside levels closely.
**Elderly:** Nephrotoxicity and ototoxicity common in the elderly; monitor and reduce dose if necessary.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies


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depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
*Not currently available in the UK.*



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# CLARITHROMYCIN

*Please note clarithromycin is not licensed for the treatment of tuberculosis in the UK*.
Clarithromycin is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

## DOSAGE

*For all patients over 12 years old:*
**By intravenous infusion:**

- 500mg twice a day given through a large proximal vein.

**By mouth:**

- 500mg twice a day.

*Paediatric doses:* [NOTE: Limited data on evidence for dosing in TB. These doses are based on clarithromycin dosing for respiratory tract infections in the latest BNF for children 2012-2013.]
**By intravenous infusion into large proximal vein**

- Child 1 month–12 years: 7.5 – 15 mg/kg twice a day
- Child 12–18 years: 500 mg twice a day

**By mouth:**
Child 1 month – 12 years:

- body-weight under 8 kg: 7.5 mg/kg twice a day
- 8–11 kg: 62.5 mg twice a day
- 12–19 kg, 125 mg twice a day
- 20–29 kg, 187.5 mg twice a day
- 30–40 kg, 250 mg twice a day

Child 12 – 18 years: 500mg twice a day

## PREPARATIONS

**Oral:** 250mg, 500mg tablets.
125mg/5mL, 250mg/5mL suspension.
**Parenteral:** 500mg powder for solution for injection

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Gastrointestinal:** Abdominal pain (2%), diarrhoea (3-6%), nausea (3%), vomiting (6%) and taste perversion (3-19%).
**Neurological**: Headache (2%).
**SERIOUS:**
**Cardiovascular:** QTc prolongation (very rare)
**Dermatological** (rare): Anaphylaxis, leukocytoclastic vasculitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome.

**Hepatic:** Hepatomegaly, hepatic dysfunction & hepatic failure (rare).
**Immunological:** Anaphylaxis.
**Infective:** Clostridium difficile-associated diarrhoea and colitis.
**Ototoxicity:** Hearing loss and tinnitus reported in association with long-term use.

## ADVERSE EFFECTS: MONITORING

**ECG:** Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
**Audiometry:** Baseline and repeat if symptomatic.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTIONS

Use with caution with antivirals:

- *Increased plasma concentrations* of: atazanavir, etravirine, nevirapine, telaprevir, tipranavir, and possibly maraviroc, rilpivirine.
- *Increased clarithromycin concentrations* with: atazanavir, ritonavir, telaprevir, tipranavir.
- *Reduced clarithromycin concentrations* with: atravirine, nevirapine.
- *Increased risk of ventricular arrhythmias* with saquinavir and telaprevir.

Increased plasma concentrations of:

- Antiepileptics: carbamazepine, phenytoin (monitor plasma concentrations).
- *Ciclosporin* (avoid clarithromycin, or monitor ciclosporin plasma concentrations).
- *Coumarins* e.g. warfarin (increased **anticoagulant** effect).
- *Ivabradine* (avoid use).
- *Linezolid* (consider drug level monitoring)
- *Rifabutin* (requires rifabutin dose reduction).
- *Sirolimus* (avoid clarithromycin, or monitor sirolimus plasma concentrations).
- *Statins* (avoid use).
- *Tacrolimus* (avoid clarithromycin, or monitor tacrolimus plasma concentrations).
- *Theophylline* (reduce theophylline dose and monitor plasma concentrations).
- *Ticagrelor* (avoid use).

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To macrolides.
**Use of other drugs that may prolong the QT interval.**
**Renal & liver disease:** Avoid in patients with both severe renal and liver disease.

**Cautions:**
**Pregnancy & Breast-feeding.**
**Renal Disease:** Use with caution. Reduce the dose.
**Myasthenia Gravis**: Macrolides may aggravate myasthenia gravis.

**Cardiovascular Disease:** Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesaemia, bradycardia (<50 bpm), or when co-administered with other medicinal products associated with QT prolongation.

## LABORATORY INFORMATION

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# CLOFAZIMINE

## DOSAGE

**Adults:** Recommend 100mg to 200mg once daily (oral).
Doses of 200mg daily for two months, then 100mg daily have been used. (Doses up to 300mg once daily have been used in leprosy).
**Children:** 2-5 mg/kg once daily. (Dose should be rounded to the nearest full capsule. This may require alternate day dosing if the dose in mg/kg/day is too high.)

Clofazimine should be taken with meals or with milk to maximise absorption and reduce gastrointestinal adverse effects.

## PREPARATIONS

**Oral:** 100mg capsules (unlicensed medicine).

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Dermatological:** Pink to brownish-black skin discoloration (resembling sun-tanning) within 1-4wks in 75-100% of patients. It gradually disappears within 6-12 months after stopping treatment. It is important to advise patients of this prior to commencing treatment.
Ichthyosis & dry skin (8-38%), pruritis (5%), rash (1-5%), photosensitivity reactions (wear protective clothing and sunscreens).
**Gastrointestinal:** (up to 50% of patients): Abdominal pain, nausea, vomiting, diarrhoea, weight loss.
**SERIOUS:**
**Gastrointestinal:** (<1%): bowel obstruction, GI haemorrhage.
**Ophthalmic:** Conjunctival pigmentation (38-57%), subjective dimness of vision (12.3%), and dry eyes, burning, and other ocular irritation (24.6%).
**Psychiatric:** Reactive depression due to skin discolouration.
**Other:** Splenic infarction, discolouration of body fluids.

## ADVERSE EFFECTS: MONITORING

*Risk of QT prolongation and ventricular tachyarrhythmias (thought to be torsades de pointes) has been highlighted in case reports.*
**ECG:** Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

May *reduce the absorption rate of rifampicin*, but is unlikely to be clinically significant.

*Isoniazid may increase plasma and urinary concentrations* of clofazimine and decrease skin concentrations.
*Increased risk of prolonged QTc* with other drugs that prolong QTc including fluoroquinolones and bedquiline.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To clofazimine.
**Hypersensitivity**: To peanuts or soya, as clofazimine capsules contain soybean oil.

**Cautions:**
**Pregnancy & Breast-feeding**
**Renal Disease:** Use with caution. Dose reductions are not necessary.
**Liver Disease**: Use with caution. Metabolised by the liver, therefore may require dose adjustment in severe liver disease.

## LABORATORY INFORMATION

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*Not currently available in the UK.*


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# CO-AMOXICLAV

## DOSAGE

**Adults**: 250mg/125mg of amoxicillin/clavulanic acid two to three times a day, given 30 minutes prior to each carbapenem dose.

**Children**: Limited data. The Sentinel Project advise 40mg/kg of amoxicillin twice a day, given 30 minutes prior to each carbapenem dose. (Maximum of 500mg per day of clavulanic acid).

## PREPARATIONS

**Oral:** 250/125mg (375mg), 500/125mg (625mg) tablets.
125/31mg, 250/62mg suspension.
**Parenteral:** 500/100mg, 1000/200mg Powder for solution for injection or infusion.

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Dermatological**: Rash & urticaria (3%).
**Gastrointestinal:** Nausea & vomiting (1-5%), diarrhoea (9%).
**Infective**: Candidiasis, particularly oral and vaginal (1%).
**SERIOUS:**
**Dermatological**: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis.
**Hepatic**: Hepatitis, cholestatic jaundice.
**Immunological**: Anaphylaxis.

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

No common serious drug interactions usually expected.
Anticoagulants: Case reports of increased INR in patients taking acenocoumarol or warfarin and prescribed a course of amoxicillin. Monitor INR.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To penicillins.
**Liver Disease:** Previous history of jaundice/hepatic impairment due to co-amoxiclav.

**Cautions:**

**Pregnancy & Breast-feeding**

**Renal Disease:** Use with caution. Reduce dose in severe renal impairment.

**Liver Disease**: Use with caution. Monitor liver function. Cholestatic jaundice may occur during or shortly after the use of co-amoxiclav. Risk is higher in patients aged >65 years and in men.

## LABORATORY INFORMATION

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# CYCLOSERINE

## DOSAGE

**Adults:** Initially 250mg twice a day (oral), increased to 500mg twice a day depending on serum concentrations.
The usual target dose in adults is 10-20mg/kg/day once or twice per day. Maximum 1g per day.
**Children:** 15-20 mg/kg once daily. Maximum 1g per day.

All patients must be prescribed pyridoxine whilst receiving cycloserine. The usual dose ranges from 50 to 100mg daily, up to 50mg per 250mg of cycloserine.

## PREPARATIONS

**Oral:** 250mg capsules.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Ensure therapeutic dose.
- Ensure toxic levels are not reached.
- Renal impairment.

**Target Level:** 20 – 35mg/L (peak).
10 – 20mg/L

**Timing of sample:**

- Peak: 3-4 hours post dose.
  - Repeat at 6 hours if suspect delayed absorption**.**
- Trough levels: taken immediately prior to a dose.

**Frequency of Levels:**

- Serum levels after 4 days at target dose.
- Repeat fortnightly for one month and until stable. Serum levels may increase over a 2-week period despite a stable dose due to accumulation of cycloserine.
- Repeat at least 6 monthly.
- Repeat if suspect malabsorption, treatment failure, or neuropsychiatric side effects (should be monitored monthly).
- *Patients with reduced renal function require more frequent monitoring, initially weekly until stable.*

**Suggested Actions:**

- **High Peak Level:** Reduce dose if level >35mg/L. If level is 35 to 50mg/L, consider reducing dose by 25% per day. If level >50mg/L, consider halving the dose. Recheck level after four days.
- **Low Peak Level**: Increase dose if level <15mg/L.
- **Trough levels:** Cyloserine absorption may be slow and consequently a 2-hour peak level may not capture the true Cmax. It is rare to see elevated peak levels in the absence of elevated trough levels, therefore a raised trough level may indicate potentially toxic 'true' peak levels. Consider serial peak serum level assays (e.g. at 2, 4 and 6 hours post dose), and dose reduction.

## ADVERSE EFFECTS

**COMMON:**
**Neurological:** Confusion, disorientation, dizziness, somnolence (increased risk if peak serum level >35mg/L).
**SERIOUS:**
**Cardiovascular**: Sudden development of congestive heart failure (rarely reported at doses greater than 1 to 1.5g daily).
**Dermatological:** Rash and photosensitivity, Stevens-Johnson syndrome (rare).
**Haematological:** Vitamin B12 and/ or folic acid deficiency, megaloblastic anaemia or sideroblastic anaemia (rare).
**Psychiatric:** Depression, seizure, psychotic disturbances (increased risk if peak serum level >35mg/L).

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Alcohol: Increased risk of convulsions with cycloserine.
Isoniazid: Increased risk of CNS toxicity when given with cycloserine.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To cycloserine.
**Neurological:** Epilepsy, depression, severe anxiety, psychotic states.
**Alcohol Dependence.**
**Renal Disease:** Severe renal impairment.

**Cautions:**
**Pregnancy & Breast-feeding**
**Neurological:** Stop or reduce dose if symptoms of central nervous system toxicity such as convulsions, psychosis, somnolence, depression, confusion, hyper-reflexia, headache, tremor, vertigo, paresis or dysarthria.
**Dermatological:** Stop or reduce dose if allergic dermatitis develops.
**Renal Disease:** Use with caution. Reduce dose in severe renal impairment.

## LABORATORY INFORMATION

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# DELAMANID

*There are limited data available on delamanid. Clinicians are advised to monitor patients closely to ensure the safe and effective use of this drug. Delamanid has additional materials to minimise the risk during use which should be read in full before initiating therapy. Access via* *http://beta.medicines.org.uk/emc/medicine/28927*

## DOSAGE

**Adults (aged 18 to 64 years):** 100mg twice a day for 24 weeks.

**Children:**

| Weight bands | Age (months) | Dose* |
|---|---|---|
| <3kg | - | Consult with Specialist |
| 3-<5kg | - | 25mg once daily |
| 5-<10kg | <3 months | 25mg once daily |
| | ≥3 months | 25mg twice daily |
| 10-<16kg | - | 25mg twice daily |
| 16-<30kg | - | 50mg once daily in the morning, followed by 25mg once daily in the evening |
| 30-<46kg | - | 50mg twice daily |
| ≥46kg | - | 100mg twice daily |

***** When available, delamanid 25mg dispersible tablets should be prioritised for young children over the 50mg tablet. Delamanid 50mg tablets dissolved in water have been shown to be bioequivalent to tablets swallowed whole.

**Elderly (>65 years of age):** No data are available in the elderly.

Delamanid should be taken with food.

## PREPARATIONS

**Oral:** 50mg tablets.

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

*There are currently limited data on adverse drug reactions cause by delamanid. Current data are based on one double-blind clinical trial in which 321 patients received delamanid in combination with an Optimised Background Regimen (OBR) to treat MDRTB. Refer to product SmPC for further information.*

**Report all suspected adverse drug reactions to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme.**

**COMMON:**



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**Dermatological**: Dermatitis & urticaria.
**Gastrointestinal:** Nausea, vomiting, diarrhoea.
**Neurological**: Dizziness, insomnia, paraesthesia, tremor
**Respiratory:** Haemoptysis
**SERIOUS:**
**Cardiovascular:** QTc prolongation (more common in hypoalbuminaemia (particularly below 2.8 g/dl), known congenital prolongation of the QTc-interval, or any condition or concomitant drug that may prolong the QTc-interval).
**Haematological**: Anaemia, eosinophilia, thrombocytopaenia, leucopaenia.
**Hepatic**: Increases in LFTs.
**Metabolic:** Hypertriglyceridaemia, hypercholesterolaemia
**Psychiatric:** Psychotic disorder, agitation, anxiety, depression, restlessness.

## ADVERSE EFFECTS: MONITORING

**ECG:** Baseline and monthly throughout treatment.

- Discontinue delamanid and all other QT prolonging drugs if the patient develops:
  - Clinically significant ventricular arrhythmia
  - A QTc interval of > 500 ms (confirmed by repeat ECG)
- If QTc interval >450ms in males, or >470 in females:
  - Monitor ECGs more frequently to confirm that the QTc interval has returned to baseline. We suggest increasing monitoring to 2 weekly.
- If syncope occurs, obtain an ECG to detect QT prolongation.

**U&Es, calcium & magnesium:** at baseline and repeated if QT prolongation is detected.
**Albumin**: Baseline and monthly throughout treatment.

- If serum albumin < 28g/L (2.8 g/dL): do not initiate treatment or continue treatment with delamanid.
- If serum albumin 28 to 34 g/L (2.8 to 3.4 g/dL): increase the frequency of ECG monitoring.

Routine tests as per generic MDR-TB treatment monitoring guidelines. (hyperlink)

## INTERACTIONS

*Many of the drugs listed below increase the risk of prolonged QT interval when used in combination with Delaminid. We therefore recommend increasing the frequency of ECG monitoring. There is no evidence for how much more frequently ECGs should be performed but we would recommend at least fortnightly for the first month and if the QTc interval remains within normal range to reduce this to monthly thereafter.*

**Anti-arrhythmics:** (e.g. amiodarone, dysopyramide, procainamide, quinidine and sotalol). Risk of prolonged QT interval**.**
**Antiretrovirals:** Limited data. lopinavir/ritonavir increases exposure to the metabolite DM-6705, which has been associated with QTc prolongation. No effect on exposure to tenofovir, lopinavir/ritonavir and efavirenz.
**Antidepressants, Tricylic:** Risk of prolonged QT interval**.**
**Antipsychotics (e.g. thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole, and pimozide).** Risk of prolonged QT interval**.**
**Antiemetics:** domperidone. Risk of prolonged QT interval.

**Azole antifungals (e.g. fluconazole, itraconazole, posaconazole, voriconazole):** Risk of prolonged QT interval.
**Ethambutol:** steady state plasma concentrations of ethambutol increased by approximately 25%. The clinical relevance is unknown.
**Fluoroquinolones (e.g. moxifloxacin):** Risk of prolonged QT interval. Moxifloxacin is not recommended for use in patients treated with delamanid. Increase frequency of ECG monitoring when delamanid is used in combination with a fluoroquinolone.
**Macrolides:** Risk of prolonged QT interval.

*This information is not inclusive of all drug interactions. Please refer to the SPC or BNF for further information, or discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**CYP3A inducers** (e.g. carbamazepine).
**Pregnancy & breast feeding.**
**Hypersensitivity:** to delamanid**.**
**Hypoalbuminaemia:** Serum albumin < 2.8 g/dL.

**Cautions:**
**Alcohol or substance misuse:** Lack of data.
**Complex extrapulmonary TB** (e.g., meningitis, osteoarthritis).
**Children aged <18 years:** The safety and effectiveness has not been established in children.
**Elderly patients ≥ 65 years:** Lack of data in patients aged 65 and over to determine whether they respond differently from younger patients.
**Cardiovascular**: Due to the risk of QT prolongation with delamanid, ECGs should be monitored closely in patients:

- Taking other QT prolonging drugs (e.g fluoroquinolones, macrolides, clofazimine)
- With a history of Torsade de Pointes, congenital long QT syndrome, hypothyroidism and bradyarrhythmias, or uncompensated heart failure
- With serum calcium, magnesium, or potassium levels below the lower limits of normal

**Diabetes:** Lack of data.
**HIV/TB co-infection**: Limited or no information on the use of delamanid.
**Liver disease:** Lack of data in moderate to severe liver disease. No dose adjustment required in mild hepatic impairment.
**Renal disease:** Lack of data for use in patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider for contact details. Turnaround time is usually a few days to a week but this can be reduced by calling ahead and informing the laboratory in advance.

# ETHAMBUTOL

## DOSAGE

**Adults:** 15mg/kg once daily (oral); **or** for DOT supervised regimen: 30mg/kg three times per week. (*Round the dose up or down to the closest whole number of tablets*).

**Obesity: It has been suggested that for markedly obese patients (consider for patients with BMI >30) should have an adjusted dose using ideal body weight:**
Use ideal body weight plus 40% of the excess weight:

- Male ideal body weight (kg) = 50 + (2.3 x height in cm above (152.4/2.54))
- Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above (152.4/2.54))

**Children (1 month to 18 years):** 15-25mg/kg once daily (oral); **or** for DOT supervised regimen: 30mg/kg three times per week. (*Doses should be rounded down to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet*).

## PREPARATIONS

**Oral:** 100mg, 400mg tablets
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).
Suspension (as a manufactured 'special' - unlicensed medicine).
An intravenous preparation may be available from specialist importers.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Known or suspected malabsorption.
- Renal impairment.
- Poor treatment response.

**Target Level:** 2 – 6mg/L *(Peak)*
**Timing of sample:**

- 2 hours post dose.
- Repeat at 6 hours if suspect delayed.

**Frequency of Levels:**

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Endocrine**: Hyperuricaemia.
**Gastrointestinal**: Nausea, vomiting.
**SERIOUS:**
**Ophthalmic**: Optic Neuritis (1-6%; greatest risk at doses >25mg/kg/day, or >2 months treatment), red/green colour blindness.

## ADVERSE EFFECTS: MONITORING

**Opthalmic**:
Visual acuity and colour discrimination testing at baseline. In addition:

- **Routine Monitoring:** For doses of 15mg/kg: A symptom screen should be undertaken monthly. Any reported visual disturbance should result in prompt referral for formal ophthalmology assessment. If no complaints of visual disturbance, visual acuity and colour discrimination should be formally tested at least 6 monthly. The WHO and ATS recommend monthly testing after two months.
- **Patients at higher risk of Opthalmic Toxicity (doses >15mg/kg OR children OR those with renal impairment):** additional vigilance is advised and we recommend monthly visual acuity, colour discrimination testing and a symptom screen.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Isoniazid: Possible increased risk of optic neuropathy caused by ethambutol.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To ethambutol.
**Ophthalmic:** Optic neuritis and poor vision unless clinical judgement determines that it may be used.

**Cautions:**
**Renal Disease:** Reduce dose in severe renal impairment.
**Young Children:** Due to difficulty in testing eyesight and obtaining reports on symptomatic visual changes.
**Elderly Patients**: Due to the risks of ophthalmic adverse effects.

## LABORATORY INFORMATION

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**Sample Type**: Serum.
**Volume Required**: 2 ml.
**Sample Container**: Plain (non SST).
**Container Type**: Any.
**Availability**: Office Hours.
**Turnaround Time**: 7 Days.

# IMIPENEM/CILASTATIN

*Please note Imipenem is not licensed for the treatment of tuberculosis in the UK*.
Imipenem is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

## DOSAGE

[NOTE: Limited data on evidence for dosing in TB]
**Adults (>50kg):** 1g twice a day (intravenous). (Dose is based on the imipenem component).
**Adults (<50kg):** 15mg/kg twice a day (intravenous). (Dose is based on the imipenem component).
**Children:** Not used in patients aged <15 years (use meropenem).

In renal failure dose reduction may be necessary. *Please discuss with a pharmacist.*

## PREPARATIONS

**Parenteral:** 500/500mg 250mg powder for solution for infusion.

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Dermatological**: Rash & urticaria (3%), injection site pain.
**Gastrointestinal:** Nausea, vomiting, diarrhoea.
**Haematologic**: Thrombophlebitis (3%), eosinophillia (4%).
**Hepatic:** Transient mild increases in LFTs.
**Renal**: Transient increases in urea and/or serum creatinine concentrations (<2%).
**SERIOUS:**
**Immunological:** Anaphylaxis.
**Infections**: Clostridium difficile-associated diarrhoea and colitis.
**Haematologic:** Pancytopaenia, neutropaenia, leucopaenia, thrombocytopaenia, thrombocytosis (rare): agranulocytosis.
**Neurological**: Seizures.
**Renal** (rare): Acute renal failure, oliguria/anuria, polyuria, urine discoloration.

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Ganciclovir: Increased risk of convulsions.
Valproate: Reduced serum concentrations of valproate. Avoid concomitant use.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** Severe hypersensitivity to penicillins, carbapenems or cephalosporins.
**Pregnancy.**

**Cautions:**
**TB Meningitis:** Increased risk of seizures. Meropenem may be preferred.
**CNS disease:** Increased risk of seizures. Meropenem may be preferred.
**Breast-feeding.**
**Renal impairment:** Increased risk of seizures, reduce dose.
**Liver disease:** Monitor LFTs (risk of increase in transaminases, hepatic failure and fulminant hepatitis).

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time for tests is usually a few days to a week but this can be reduced by calling ahead and informing the laboratory in advance.



The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

# ISONIAZID

## DOSAGE

**Adults:** 300mg once a day (oral or intravenous). Consider 5mg/kg once a day if low body weight (oral or intravenous); **or** for DOT supervised regimen: 15mg/kg three times a week (oral).

**Children:** 10mg/kg (max. 300mg) once a day (oral or intravenous); **or** for DOT supervised regimen: 15mg/kg (max. 900mg) three times a week (oral).
Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet.
Isoniazid should be taken 30-60 minutes before food, or 2 hours after food.

**Low level isoniazid resistance:**

**Children:** 15-20mg/kg once a day
**Adults:** Doses of 16-18mg/kg once a day have been used.

Pyridoxine can be used to reduce the risk of peripheral neuropathy in all patients taking isoniazid. In particular it should be prescribed for those most at-risk, such as patients with diabetes, alcohol abuse or malnutrition.

All patients prescribed high-dose isoniazid must also be prescribed pyridoxine as there is an increased risk of peripheral neuropathy.

## PREPARATIONS

**Oral:** 100mg capsules.
Liquid (as a manufactured 'special' - unlicensed medicine).
Rifinah® 300/150 tablets (rifampicin 300mg, isoniazid 150mg).
Rifinah® 150/100 tablets (rifampicin 150mg, isoniazid 100mg).
Rifater tablets (rifampicin 120mg, isoniazid 50mg, pyrazinamide 300mg).
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).

**Paediatric oral fixed dose combinations (dissolvable in water):**

| Weight | Number of tablets | |
|---|---|---|
| | **Intensive phase RHZ 75/50/150 *** | **Continuation phase RH 75/50** |
| 4-7 kg | 1 | 1 |
| 8-11 kg | 2 | 2 |
| 12-15 kg | 3 | 3 |
| 16-24 kg | 4 | 4 |
| ≥25kg | Adult dose recommended | Adult dose recommended |

***Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.*



The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

**Parenteral:** 50mg/2mL ampoules.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Known or suspected malabsorption.
- Poor treatment response.

**Target Level:** 3 – 5mg/ L *(Peak).*

**Timing of sample:**

- 2 hours post dose.
- Repeat at 6 hours if suspect delayed absorption**.**

**Frequency of Levels:**

- Drug levels need not be routinely measured.

**Adherence Monitoring**

INH strips can be used to measure adherence to isoniazid treatment.

- BBL Taxo INH Test Strips are absorbent paper strips that colour green, blue or purple in the presence of isonicotinic acid (a metabolite of isoniazid)
- BBL Taxo INH Test Control is an isoniazid-impregnated disc that will yield a positive result in the test procedure.

## ADVERSE EFFECTS

**COMMON:**

**Neurological:** Peripheral Neuropathy.
**Hepatic:** Transient increases in LFTs.

**SERIOUS:**

**Dermatological**: Skin reactions e.g. urticaria (uncommon).
**Haematologic:** Agranulocytosis, megaloblastic anaemia, thrombocytopaenia.
**Hepatic:** Hepatotoxity (rare).
**Immunological:** Drug-induced lupus (rare).
**Musculoskeletal**: Arthralgia, rhabdomyolysis.
**Neurological:** Seizure, psychosis (rare).

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Carbamazepine: increased plasma concentration of carbamazepine. Increased risk of hepatoxicity.
Food: Reduced absorption. Take isoniazid 30-60 minutes before food, or 2 hours after food.
Food: Possible increased risk of headache, sweating, palpitations, flushing, hypotension when eating certain foods such as cheese, skipjack tuna or other tropical fish, or red wine. Usually, no dietary restrictions are required unless symptoms are experienced. This reaction is thought to be due to the high histamine or tyramine content of these foods and drink, resulting in an exaggerated histamine poisoning reaction due to inhibition of histamine metabolism by isoniazid, or the sympathomimetic action of tyramine due to inhibition of mono-amine oxidase by isoniazid.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To isoniazid.

**Cautions:**
**Liver disease, alcohol abuse, hepatitis B co-infection:** monitor LFTs closely.
**Malnutrition, HIV co-infection, diabetes mellitus, and alcohol dependence**: Increased risk of peripheral neuropathy; prescribe prophylactic pyridoxine.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
**Sample Type**: Plasma.
**Volume Required**: 2 ml.
**Sample Container**: Fluoride Oxalate.
**Container Type**: Any.
**Availability**: Office Hours.
**Turnaround Time**: 7 Days.

# LEVOFLOXACIN

*Please note levofloxacin is not licensed for the treatment of tuberculosis in the UK*.

- Despite the lack of data establishing the safety and efficacy of fluoroquinolone use in children they continue to be used to treat MDR-TB in children of all ages in clinical practice. It is felt the benefit of treatment of MDR-TB outweighs the small potential risk of adverse reactions.
- If using a flouroquinolone we would recommend moxifloxacin as first choice agent followed by levofloxacin.

## DOSAGE

**Adults:** 10–15 mg/kg once daily (usually 750mg to 1000mg once daily).
**Children:** 15-20mg/kg once daily.

## PREPARATIONS

**Oral:** 250mg, 500mg tablets.
**Parenteral:** 400mg/100mL solution for infusion.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Known or suspected malabsorption.
- Poor treatment response.

**Target Level:** 8 – 12mg/L *(peak).*
0.5 – 2 mg/L *(trough).*

**Timing of sample:**

- 2 hours post oral dose (or 1 hour after the end of intravenous infusion).
- Repeat at 6 hours if suspect delayed absorption**.**
- Consider taking a trough level.

**Frequency of Levels:**

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Gastrointestinal**: Nausea, vomiting, diarrhoea.
**Other:** Dizziness, headache.
**Hepatic**: Transient increases in LFTs.
**SERIOUS:**
**Cardiovascular:** QTc prolongation (rare; more common in hypokalaemia, and predisposing cardiac conditions).
**Dermatological:** Stevens-Johnson syndrome or toxic epidermal necrolysis (rare).
**Metabolic:** Hypoglycaemia (in patients on hypoglycaemic drugs, uncommon).
**Haematologic:** Eosinophilia, leucopaenia (uncommon), thrombocytopaenia, neutropaenia (rare).
**Hepatic:** Acute hepatitis (rare).
**Immunological**: Anaphylaxis, immune hypersensitivity (uncommon).
**Musculoskeletal:** Tendon inflammation and rupture (see contra-indications below).

**Neurological:** Seizures (caution in patients with CNS disorders).
**Renal:** Renal impairment (rare).

## ADVERSE EFFECTS: MONITORING

**ECG:** Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
**LFTs, U&Es and FBC** should also be monitored sporadically throughout treatment. No specific frequency recommendations but generic monitoring guidelines should be frequent enough.
Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Amiodarone: Increased risk of ventricular arrhythmia.
Antacids: Reduced absorption of levofloxacin.
Anticoagulants: Possible enhanced effect of coumarins (e.g. warfarin) and phenindione.
Ciclosporin: Increased risk of nephropathy.
Iron: Reduced absorption of levofloxacin.
NSAIDS: Possible increased risk of convulsions.
Theophylline: Increased risk of convulsions. Reduce dose of theophylline and monitor levels.
Zinc: Reduced absorption of levofloxacin.
Drugs known to prolong the QT interval: use with caution in patients taking Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To levofloxacin or other quinolones.
**Epilepsy/Seizure Activity:** May induce convulsions in patients with or without history of convulsions, use with caution if epileptic or conditions predisposing seizures.
**Tendon Damage:** Rarely reported but damage or rupture may occur within 48 hours of treatment and several months after stopping treatment. Increased risk in patients with a history of tendon disorders related to quinolone use, aged over 60 years, concomitant use of corticosteroids. Cease all quinolone treatment if tendinitis suspected.
**Pregnancy**: Avoid in pregnancy, animal studies have shown quinolones cause arthropathy.
**Breast Feeding:** Avoid, present in milk in animal studies.
**Children:** Levofloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in TB with caution. Arthropathy has developed in weight-bearing joints in young animals.

**Cautions:**
**May impair performance of skilled tasks such as driving**
**Long QT Syndrome:** Can prolong QT interval. Use with caution in patients with risk factors for QT interval prolongations.
**Myasthenia Gravis:** Risk of exacerbation.
**G6PD deficiency:** Risk of haemolytic reactions when treated with quinolones.
**Liver Disease:** Monitor LFTs.
**Renal Disease**: Reduce dose in renal impairment.
**Sunlight:** Risk of photosensitivity reaction.

**Serious bullous skin reactions:** Risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.
**Peripheral Neuropathy:** Sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
**Sample Type**: Serum.
**Volume Required**: Ideally 2ml (min 0.1mL).
**Sample Container**: Plain glass or plastic (non SST).
**Container Type**: Any.
**Availability**: NS.
**Turnaround Time**: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post
The sample must be heat-treated before dispatch if HIV positive.
**Please telephone at least one day in advance of the sample.**


The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

# LINEZOLID

*Please note linezolid is not licensed for the treatment of tuberculosis in the UK*.
Linezolid is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

## DOSAGE

By mouth or intravenous infusion.
**Adults:** 600mg once a day (oral or intravenous). Consider reducing to 300mg once daily if serious adverse effects develop.
**Children 1-15kg:** 15mg/kg once daily
**Children 16kg+:** 10-12mg/kg once daily (maximum 600mg in 24 hours)

## PREPARATIONS

**Oral:** 600mg tablets.
100mg/5mL granules for oral suspension.
**Parenteral:** 600mg/300mL solution for infusion.

## DRUG LEVEL MONITORING

**Indications for monitoring:**
- Known or suspected malabsorption.
- Poor treatment response.

**Target Level:** 12-24 mg/L (*peak).*
**Timing of sample:**
- 2 hours post-oral dose or 1 hour post IV infusion.

**Frequency of Levels:**
- No need for regular monitoring.

## ADVERSE EFFECTS

**COMMON:**
**Gastrointestinal**: Diarrhoea (4%), nausea (3%), vomiting.
**Neurological**: Headache (2%).
**Infections**: Candidiasis, particularly oral and vaginal (1%).
**Hepatic**: Transient increases in LFTs.
**SERIOUS:**
**Metabolic**: Lactic acidosis.
**Dermatological**: Urticaria, rash; (rare): Bullous disorders such as Stevens-Johnson syndrome & toxic epidermal necrolysis.
**Haematologic:** Myelosupression.
**Neurological**: Peripheral neuropathy, seizure, serotonin syndrome.
**Ophthalmic**: Optic neuropathy – increased risk with prolonged treatment.

## ADVERSE EFFECTS: MONITORING

**FBC:** Check FBC at baseline, then every two weeks for one month, then monthly.

**Lactate:** Consider measuring a lactate in those with symptoms of lactic acidosis such as nausea, vomiting, weightloss, hyperventilation,and tachypnea. Evidence to suggest risk of lactic acidosis increases after 6 weeks on Linezolid.

**VISUAL ACUITY & COLOUR DISCRIMINATION:** Ask patients whether there have been any changes to their vision, and consider performing visual acuity and colour discrimination testing (Snellen & Ishihara charts) every month. Refer to ophthalmology if necessary.

**PERIPHERAL NEUROPATHY:** Encourage patients to report any symptoms suggestive of peripheral neuropathy and arrange nerve conduction studies should these arise.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

*Clarithromycin:* increases linezolid serum levels with risk of toxicity (consider drug level monitoring).

Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, linezolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, $5HT_1$ agonists ('triptans'), tricyclic antidepressants, sympathomimetics, dopaminergics, buspirone, pethidine and possibly other opioid analgesics.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To linezolid.
**Mono-amine oxidase inhibitors:** Avoid concomitant use of other drugs that inhibit monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any such medicinal product.
**Avoid in patients with:** Uncontrolled hypertension, phaechromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia or acute confusional states.
**Breast-feeding**

**Cautions:**
**Pregnancy**
**Avoid:** Consumption of large amounts of tyramine rich foods.
**Epilepsy/history of seizures:** Increased risk of convulsions.

**Renal impairment:** No dose adjustment is required. However two primary metabolites may accumulate in severe renal impairment, but the clinical significance of this is unknown. Use with caution and monitor for adverse effects closely (see above).
**Liver disease:** No dose adjustment is required. However due to limited clinical data, use with caution and monitor for adverse effects closely (see above).
**Peripheral and optic neuropathy:** Patients should be advised to report symptoms of visual impairment.

## LABORATORY INFORMATION

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**Sample Type**: Serum.
**Volume Required**: 2ml (min 0.1mL).
**Sample Container**: Plain plastic (non SST).
**Container Type**: Any.
**Availability**: NS
**Turnaround Time**: Telephoned same day if received 9am-3pm Mon-Fri. Written confirmation report will be sent by 1st Class post.
The sample must be heat-treated before dispatch if HIV positive.
**Please telephone at least one day in advance of the sample**.

# MEROPENEM

*Please note meropenem is not licensed for the treatment of tuberculosis in the UK*.
Meropenem is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

## DOSAGE

**Adults:**

- 1g three times a day (intravenous).
- NB. Should be used in combination with clavulanate in the form of a combination of co-amoxiclav 625mg (500 mg/125 mg) three times a day.

**Children:**

- Adult dose in weights over 50Kg.
- 1 month–14 years: 20–40 mg/kg every 8 hours (intravenous).

**Maximum dose:** 6000mg/ day

In renal failure dose reduction may be necessary. *Please discuss with a pharmacist.*

## PREPARATIONS

**Parenteral:** 500mg, 1g powder for solution for injection or infusion.

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Dermatological**: Rash, pruritis, injection site inflammation (2%).
**Gastrointestinal:** Abdominal pain, diarrhoea (3-7%), nausea & vomiting (3%).
**Haematological**: Thrombocythaemia.
**Hepatic:** Transient increases in LFTs.
**Neurological**: Headache (2-8%).
**SERIOUS:**
**Dermatological:** Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.
**Haematological**: Eosinophilia, thrombocytopaenia, leucopaenia, neutropaenia.
**Immunological**: Anaphylaxis, angioedema.
**Infective**: Clostridium difficile-associated diarrhoea and colitis.
**Neurological**: Seizures.

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Valproate: Reduced serum concentrations of valproate. Avoid concomitant use.

*Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To carbapenems.
**Hypersensitivity:** Severe hypersensitivity to penicillins or cephalosporins.
**Pregnancy**

**Cautions:**
**Breast-feeding.**
**Liver disease:** Monitor LFTs (hepatic dysfunction with cholestasis and cytolysis).

## LABORATORY INFORMATION

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# MOXIFLOXACIN

*Please note moxifloxacin is not licensed to treat tuberculosis in the UK.*

*Despite the lack of data establishing the safety and efficacy of fluoroquinolone use in children they continue to be used to treat MDR-TB in children of all ages in clinical practice. It is felt the benefit of treatment of MDR-TB outweighs the small potential risk of adverse reactions.*

## DOSAGE

**Adults:** 400mg once a day (oral or intravenous).

***WHO recommendations for MDR-TB short course regimen (safety of the higher doses not verified)***

Weight <30kg: 400mg once a day
Weight 30-50kg: 600mg once a day
Weight >50Kg: 800mg once a day

**Children:**

10-15mg/kg once a day (oral)
Use 10mg/kg in children <6 moths old

## PREPARATIONS

**Oral:** 400mg tablets.
**Parenteral:** 400mg/250mL solution for infusion.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Known or suspected malabsorption.
- Poor treatment response.

**Target Level**

- Peak level: : 3-5mg/L
- Trough level: 0.3-0.7mg/L

**Timing of sample:**

- Peak – 2 hours post dose
  - Repeat at 6 hours if suspect delayed absorption**.**
- Consider Trough levels only if suspect delayed absorption – taken immediately prior to a dose.

**Suggested Actions:**

- **High Peak Level:** Monitor for side effects and check ECG. If tolerated, consider continuing usual dose.
- **Low Peak Level:** Repeat serum levels at 2 hours and 6 hours post dose, and trough serum level (trough level may only be required if adult patients take >400mg once daily).



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If peak level continues to be low, check adherence. Consider increasing dose (e.g. 600mg daily for weight 30-50kg, 800mg daily for weight >50kg)

- **Trough levels:** a low trough level may confirm a low peak serum level, which may require an increase in moxifloxacin dose.

**Frequency of Levels:**

- No need for regular monitoring.

## ADVERSE EFFECTS

**COMMON:**

**Cardiovascular:** QTc prolongation (more common in hypokalaemia, proarrhythmic conditions, in combination with other drugs that prolong the QT interval such as ondansetron).
**Gastrointestinal**: Nausea, vomiting, diarrhoea.
**Hepatic**: Transient increases in LFTs.
**Other:** Dizziness, headache.

**SERIOUS:**

**Cardiovascular:** QTc prolongation (rare; more common in hypokalaemia, and predisposing cardiac conditions).
**Dermatological:** Stevens-Johnson syndrome or toxic epidermal necrolysis (rare).
**Haematological:** (Uncommon) agranulocytosis, aplastic anaemia, haemolytic anaemia, thrombocytopaenia.
**Hepatic:** Acute hepatitis (rare).
**Immunological**: Anaphylaxis, immune hypersensitivity (uncommon).
**Metabolic:** Hypoglycaemia (in patients on hypoglycaemic drugs, uncommon).
**Musculoskeletal:** Tendon inflammation and rupture (see contra-indications below).
**Neurological: Seizures**: (Caution in patients with CNS disorders).
**Renal:** Renal impairment (rare).
**Respiratory:** Extrinsic allergic alveolitis (rare).
**Other:** Serum sickness (rare).

## ADVERSE EFFECTS: MONITORING

**ECG:** Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
**LFTs, U&Es and FBC** should be monitored sporadically throughout treatment. No specific frequency recommendations, please see generic monitoring guidelines for further information.
**Blood glucose** should be monitored regularly in patients with diabetes (risk of hypoglycaemia).
Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Antacids: Reduced absorption of moxifloxacin.
Anti-arrhythmics: Increased risk of ventricular arrhythmias with amiodarone or disopyramide.
Antidepressants: Increased risk of ventricular arrhythmias with tricyclics.
Antimalarials: Increased risk of ventricular arrhythmias with chloroquine, hydroxychloroquine, mefloquine, quinine.
Antipsychotics: Increased risk of ventricular arrhythmias with benperidol, droperidol, haloperidol, phenothiazines, pimozide and zuclopenthixol.

Antivirals: Increased risk of ventricular arrhythmias with saquinavir.
Beta-blockers: Increased risk of ventricular arrhythmias with sotalol.
Ciclosporin: Increased risk of nephropathy.
Erythromycin: Increased risk of ventricular arrhythmias when erythromycin given via intravenous route.
Iron: Reduced absorption of moxifloxacin.
NSAIDS: Possible increased risk of convulsions.
Pentamidine: Increased risk of ventricular arrhythmias.
Theophylline: Increased risk of convulsions. Reduce dose of theophylline and monitor levels.
Zinc: reduced absorption of moxifloxacin.
Drugs known to prolong the QT interval: use with caution in patients taking Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To moxifloxacin or other quinolones.
**Tendon Damage:** Rarely reported but damage or rupture may occur within 48 hours of treatment and several months after stopping treatment. Increased risk in patients with a history of tendon disorders related to quinolone use, aged over 60 years, concomitant use of corticosteroids. Cease all quinolone treatment if tendinitis suspected.
**Pregnancy**: Avoid in pregnancy, animal studies have shown quinolones cause arthropathy.
**Breast Feeding:** Avoid, present in milk in animal studies.
**Children:** Moxifloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in TB with caution. Arthropathy has developed in weight-bearing joints in young animals.
**Cardiovascular**: Due to the risk of QT prolongation with moxifloxacin, is should not be used in patients with congenital or documented acquired QT prolongation, clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, previous history of symptomatic arrhythmias, or electrolyte disturbances, particularly in uncorrected hypokalaemia.
**Liver disease**: Chronic liver disease; particularly Child Pugh severity score C and in those patients with transaminase levels 5 fold greater than the upper limit of normal. Consider using Levofloxacin as an alternative in these patients.
**Concurrent use with other drugs that prolong the QT interval.**

**Cautions:**
**May impair performance of skilled tasks such as driving**
**Myasthenia Gravis:** Risk of exacerbation.
**G6PD deficiency:** Risk of haemolytic reactions when treated with quinolones.
**Sunlight:** Risk of photosensitivity reaction.
**Epilepsy/Seizure Activity:** May induce convulsions in patients with or without history of convulsions, use with caution if epileptic or conditions predisposing seizures.
**Liver Disease:** Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported.
**Serious bullous skin reactions:** Risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.
**Peripheral Neuropathy:** Sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
**Sample Type**: Serum.
**Volume Required**: 2ml (min 0.1mL).
**Sample Container**: Plain glass or plastic (non SST).
**Container Type**: Any.
**Availability**: NS.
**Turnaround Time**: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.
**Please telephone at least one day in advance of the sample.**


The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

# OFLOXACIN

Please note ofloxacin is not licensed to treat tuberculosis in the UK.

- Despite the lack of data establishing the safety and efficacy of fluoroquinolone use in children they continue to be used to treat MDR-TB in children of all ages in clinical practice. It is felt the benefit of treatment of MDR-TB outweighs the small potential risk of adverse reactions.
- If using a flouroquinolone we would recommend moxifloxacin as first choice agent followed by levofloxacin.

## DOSAGE

**Adults:** 400mg twice a day (oral or intravenous).
**Children:** 15-20 mg/kg (max. 400mg) once daily (oral).

## PREPARATIONS

**Oral:** 200mg, 400mg tablets.
**Parenteral:** 200mg/100ml solution for infusion.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Known or suspected malabsorption.
- Poor treatment response.

**Target Level:** Unknown.
**Timing of sample:**

- 2 hours post oral dose (or 1 hour after the end of intravenous infusion).
- Repeat at 6 hours if suspect delayed absorption**.**
- Consider taking a trough level.

**Frequency of Levels:**

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Gastrointestinal**: Nausea, vomiting, diarrhoea.
**Other:** Dizziness, headache.
**Hepatic**: Transient increases in LFTs.
**SERIOUS:**
**Cardiovascular:** QTc prolongation (rare; more common in hypokalaemia, and predisposing cardiac conditions).
**Dermatological:** Stevens-Johnson syndrome or toxic epidermal necrolysis (rare).
**Metabolic:** Hypoglycaemia (in patients on hypoglycaemic drugs, uncommon).
**Haematological:** Eosinophilia, leucopaenia (uncommon), thrombocytopaenia, neutropaenia (rare).
**Hepatic:** Acute hepatitis (rare).
**Immunological**: Anaphylaxis, immune hypersensitivity (uncommon).
**Musculoskeletal:** Tendon inflammation and rupture (see contra-indications below).
**Neurological:** Seizures (caution in patients with CNS disorders).

**Renal:** Renal impairment (rare).

## ADVERSE EFFECTS: MONITORING

**ECG:** Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
**LFTs, U&Es and FBC** should also be monitored sporadically throughout treatment. No specific frequency recommendations but generic monitoring guidelines should be frequent enough.
**Blood glucose** should be monitored regularly in patients with diabetes (risk of hypoglycaemia).

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Antacids: Reduced absorption of ofloxacin.
Anticoagulants: Possible enhanced effect of coumarins (e.g. warfarin).
Ciclosporin: Increased risk of nephropathy.
Iron: Reduced absorption of ofloxacin.
NSAIDS: Possible increased risk of convulsions.
Theophylline: Increased risk of convulsions. Reduce dose of theophylline and monitor levels.
Zinc: Reduced absorption of ofloxacin.
Drugs known to prolong the QT interval: Use with caution in patients taking Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To levofloxacin or other quinolones.
**Epilepsy/Seizure Activity:** May induce convulsions in patients with or without history of convulsions, use with caution if epileptic or conditions predisposing seizures.
**Tendon Damage:** Rarely reported but damage or rupture may occur within 48 hours of treatment and several months after stopping treatment. Increased risk in patients with a history of tendon disorders related to quinolone use, aged over 60 years, concomitant use of corticosteroids. Cease all quinolone treatment if tendinitis suspected.
**Pregnancy**: Avoid in pregnancy, animal studies have shown quinolones cause arthropathy.
**Breast Feeding:** Avoid, present in milk in animal studies.
**Children:** Levofloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in TB with caution. Arthropathy has developed in weight-bearing joints in young animals.
**G6PD deficiency:** Risk of haemolytic reactions when treated with quinolones.

**Cautions:**
**May impair performance of skilled tasks such as driving.**
**Long QT Syndrome:** Can prolong QT interval. Use with caution in patients with risk factors for QT interval prolongations.
**Myasthenia Gravis:** Risk of exacerbation.
**Liver Disease:** Monitor LFTs.
**Renal Disease**: Reduce dose in renal impairment.
**Sunlight:** Risk of photosensitivity reaction

**Serious bullous skin reactions:** Risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.
**Peripheral Neuropathy:** Sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
**Sample Type**: Serum.
**Volume Required**: 2ml (min 0.1mL).
**Sample Container**: Plain glass or plastic (non SST).
**Container Type**: Any.
**Availability**: NS.
**Turnaround Time**: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.
**Please telephone at least one day in advance of the sample.**

# P-AMINOSALICYLIC ACID (PAS)

*Please note p-aminosalicylic acid is not licensed in the UK.*

## DOSAGE

**Adults:** 150mg/kg/day in two to four divided doses (oral). Usual dose is 8-12g per day.
**Children:** 200-300mg/kg/day (see dose banding table below for children weighing up to 30kg).

| Body Weight | Dose GranuPAS®/ Paser® |
|---|---|
| 5kg | 500mg twice daily |
| 6-7kg | 750mg twice daily |
| 8-10kg | 1000mg twice daily |
| 11-14kg | 1500mg twice daily |
| 15-18kg | 2000mg twice daily |
| 19-22kg | 2500mg twice daily |
| 23-26kg | 3000mg twice daily |
| 27-30kg | 3500mg twice daily |

**Note:** P-aminosalicyclic acid is only available in 4g sachets. The GranuPAS® brand comes with a dosage scoop graduated in milligrams to aid dosing in children. If Paser® is used, a scoop is not available. In order to give part of a sachet, flatten out the packet, so that the granules are spread evenly in the packet. Cut the packet to the approximate dose required – i.e. cut into halves for 2g doses, and into quarters for 1g doses. Discard the remaining unused portions of the packet.

The GranuPAS®/ Paser® brand of p-aminosalicyclic acid should be prescribed, since these have an acid-resistant coating, preventing stomach gastric acid from degrading the drug to m-aminophenol, a known hepatotoxin. The enteric coating therefore prevents acid degradation of the drug in the stomach, and releases the drug in the small intestine where neutral pH causes fast dissolution of the enteric coating.

The granules of p-aminosalicyclic acid should be sprinkled on to an acidic food such as applesauce or yogurt, or mixed in acidic juices such as tomato, grape, grapefruit, cranberry, apple, or orange. The granules must not be chewed, and must not be mixed with neutral pH food or drink.

Take p-aminosalicyclic acid with food to reduce gastrointestinal adverse effects.

## PREPARATIONS

**Oral:** 4g granules per sachet (unlicensed medicine).

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**

**Gastrointestinal:** Nausea, vomiting, diarrhoea, abdominal pain.
**Immunological**: Hypersensitivity reactions (5-10%) including rash & fever.
**SERIOUS:**
**Metabolic:** Hypothyroidism.
**Haematological:** Haemolytic anaemia (patients with G6PD deficiency), agranulocytosis, eosinophilia, leucopaenia, and thrombocytopaenia.
**Hepatic:** Acute hepatitis (rare).

## ADVERSE EFFECTS: MONITORING

**TFTs:** 3 monthly (if being given in combination with prothionamide, increase to monthly)
Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Antacids: Fast dissolution of acid-resistant coating, resulting in early release of p-aminosalicyclic acid into the stomach. However as the stomach gastric acid will have been neutralised, degradation of p-aminosalicyclic acid to m-aminophenol will not occur. No dose adjustments required, however administration of p-aminosalicyclic acid in acidic food or drinks is not required.
Digoxin: Possible decrease in digoxin absorption. Monitor digoxin serum concentrations.
Prothionamide: increased risk of hypothyroidism, possible increased risk of hepatoxicity.
Rifamycins: reduced absorption of rifamycins. Give 8-12 hours apart.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To p-aminosalicylic acid, or to aspirin.
**Renal Disease:** Manufacturer advises to avoid in severe renal failure, as an inactive metabolite is renally excreted. May worsen acidosis and/or crystalluria in severe renal failure.

**Cautions:**
**Pregnancy:** Use in pregnancy has not been studied/
**Breast-feeding:** P-aminosalicylic acid is secreted into breast milk at 1/70$^{th}$ of the maternal plasma concentration.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.

# PRETOMANID

*Please note pretomanid is not licensed for the treatment of tuberculosis in the UK.*
*NHS England commmissioing is anticipated Mid-2024*
*It may be imported into the UK via Tanner CH or specialist importer.*

## DOSAGE

By mouth:

**Adults and adolescents aged 14 years and older:** 200mg once daily for 26 weeks as part of BPaLM / 39 weeks as part of BPaL regimen.

**Paediatric dose**: The safety and efficacy of pretomanid in children and adolescents have not yet been established

Pretomanid should be taken with food and should be swallowed with water.

## PREPARATIONS

**Oral:** 2O0mg tablets

## DRUG LEVEL MONITORING

- Not currently available

## ADVERSE EFFECTS

**COMMON:**
The most frequent adverse drug reactions when pretomanid is used in combination with bedaquiline and linezolid were nausea (36%), vomiting (28%) and transaminases increased (21%).
**Gastrointestinal**: Nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation, decreased appetite
**Neurologic**: peripheral neurpathy, headache, dysgeusia, dizziness
**Hepatic**: transient increases in transaminases, hyperbilirubinaemia
**Dermatologic**: rash, acne, pruritis, dry skin

**SERIOUS:**
Serious adverse drug reactions when pretomanid is used in combination with bedaquiline and linezolid were peripheral neuropathy (81%) and anaemia (37%), which occur with linezolid. Serious adverse drug reactions that are considered attributable to linezolid are marked with *.
**Endocrine**: lactic acidosis*
**Haematologic:** Myelosupression*
**Neurologic** : peripheral neuropathy*
**Ophthalmic**: optic neuropathy*
**Cardiac**: prolonged QTc interval

## ADVERSE EFFECTS: MONITORING

**LFT:** At baseline, then weekly for one month, fortnightly for one month, then monthly. Treatment interruption is recommended if:

- Aminotransferase elevations are accompanied by total bilirubin elevation greater than 2 times the upper limit of normal.
- Aminotransferase elevations are greater than 8 times the upper limit of normal.
- Aminotransferase elevations are greater than 5 times the upper limit of normal and persist beyond 2 weeks

**FBC:** Due to combination treatment with linezolid, check FBC at baseline, then every two weeks for one month, then monthly.
**Potassium, Calcium and Magnesium:** Check at baseline. Repeat if prolonged QTc occurs.
**VISUAL ACUITY & COLOUR DISCRIMINATION:** Encourage patients to report any changes to their vision and refer to ophthalmology if any reported. Routine monitoring 6 monthly.
**ECG:** At baseline, then monthly. Discontinue BPaLM regimen if the patient develops a clinically significant ventricular arrhythmia or a QTcF interval of greater than 500 ms (confirmed by repeat ECG).

## INTERACTONS

**Benzylpenicillin**: Pretomanid inhibits OAT3 transporter, which nay result in increased concentrations of benzylpenicillin
**Ciprofloxacin** Pretomanid inhibits OAT3 transporter, which nay result in increased concentrations of ciprofloxacin
**CYP3A4 inducers (e.g. efavirenz, etravirine, rifamycins including rifampicin, rifapentine and rifabutin, carbamazepine, phenytoin, St. John's wort):** Avoid co-administration due to expected acceleration of pretomanid metabolism, resulting in reduced effect
**Efavirenez** accelerated metabolism of pretomanid resulting in reduced effect. Avoid co-administration.
**Indomethacin**: Pretomanid inhibits OAT3 transporter, which nay result in increased concentrations of indomethacin
**Methotrexate**: Pretomanid inhibits OAT3 transporter, which nay result in increased concentrations of methotrexate
**Paclitaxel**: accelerated metabolism of paclitaxel
**Rifampicin** accelerated metabolism of pretomanid resulting in reduced effect. Avoid co-administration.
**Warfarin**: accelerated metabolism of warfarin. Monitor INR
**BCRP substrates (e.g. rosuvastatin, prazosin, glyburide, sulfasalazine):** Pretomanid inhibits BCRP and may increase their exposure. Monitor for drug-related adverse reactions
**OATP1B3 substrates (e.g., valsartan, statins):** Pretomanid inhibits OATP1B3 and may increase their exposure. Monitor for drug-related adverse reactions
**P-gp substrates (e.g. digoxin, dabigatran etexilate, verapamil):** Pretomanid inhibits P-gp and may increase their exposure. Monitor for drug-related adverse reactions

*This information is not inclusive of all drug interactions. Please refer to the SPC or BNF for further information, or discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contra-indications**
**Hypersensitivity** to pretomanid or other nitroimidazoles
**Galactose intolerance, total lactase deficiency or glucose-galactose malabsorption**

**Children <14 years:** The safety and effectiveness has not been established in children

**Cautions:**
**Pregnanacy:** Very limited data. Pretomanid should be used during pregnancy only if the benefit to the patient is considered to outweigh the potential risk to the foetus.
**Breastfeeding:** It is unknown whether pretomanid/metabolites are excreted in human milk.
**Renal disease:** The safety and efficacy of pretomanid in populations with hepatic impairment have not been established. Use in patients with renal impairment is not recommended.
**Hepatic disease:** The safety and efficacy of pretomanid in populations with hepatic impairment have not been established.

**LABORATORY INFORMATION**
n/a

# PROTHIONAMIDE

*Please note prothionamide is not licensed in the UK.*
Prothionamide is a thioamide, and is considered to be interchangeable with ethionamide (currently not available in the UK).

## DOSAGE

*Adult & paediatric doses are the same per kg.*

**Adults:** 15-20mg/kg (max. 1g) once daily (oral).
Once daily dosing is preferred to maximise peak levels, particularly for daily doses ≤750mg. Consider twice daily dosing if patients are unable to tolerate once daily regimens.

**Children:** 15-20mg/kg (max. 1g) once daily (oral).
Once daily dosing is preferred to maximise peak levels, particularly for daily doses ≤750mg. Consider twice daily dosing if patients are unable to tolerate once daily regimens.

Prothionamide should be taken with or after meals to reduce gastrointestinal adverse effects. Most patients also require gradual dose escalation, i.e. for adults: initially 250mg once a day, increasing by 250mg every 3 to 5 days.

All patients must be prescribed pyridoxine whilst receiving prothionamide. The usual adult dose ranges from 50 to 100mg daily, up to 50mg per 250mg of prothionamide.

## PREPARATIONS

**Oral:** 250mg tablets (unlicensed medicine).

## DRUG LEVEL MONITORING

- Not required.

## ADVERSE EFFECTS

**COMMON:**
**Hepatic**: Transient increases in LFTs.
**Gastrointestinal**: Nausea, vomiting, diarrhoea, anorexia, excessive salivation, metallic taste, stomatitis, and abdominal pain.
**SERIOUS:**
**Hepatic**: Acute hepatitis (rare).
**Neurological** (maybe increased in combination with cycloserine): Dizziness, encephalopathy, peripheral neuropathy.
**Ophthalmic:** Optic Neuritis (rare).
**Psychiatric:** Psychotic disturbances, depression.
**Metabolic**: Gynaecomastia, hypoglycaemia, hypothyroidism.

## ADVERSE EFFECTS: MONITORING

**TFTs:** 3 monthly (if being given in combination with PAS increase to monthly).
**Blood glucose** should be monitored regularly in patients with diabetes (risk of hypoglycaemia).
Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Cycloserine: possible increased risk of neurotoxicity.
Isoniazid: increased serum concentrations.
P-aminosalicylic acid: increased risk of hypothyroidism, possible increased risk of hepatoxicity.
Rifampicin: increased risk of hepatoxicity.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To ethionamide or prothbionamide.
**Severe Liver Disease:** Due to risk of further hepatotoxicity.
**Pregnancy.**
**Porphyria.**

**Cautions:**
**Renal Disease:** Reduce dose in severe renal impairment.
**Breast-feeding.**

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.

# PYRAZINAMIDE

## DOSAGE

**Adults (<50kg):** 1.5g once a day (oral); **or** for DOT supervised regimen: 2g three times a week (oral).
**Adults (50kg+):** 2g once a day (oral); **or** for DOT supervised regimen: 2.5g three times a week (oral).
**Children:** 30-40mg/kg once daily (max. 1.5g if <50kg; 2g if 50kg+) once a day (oral); **or** for DOT supervised regimen: 50mg/kg (max. 2g if <50kg; 2.5g of 50kg+) three times a week (oral). (*Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet*)

Pyrazinamide may be taken with or without food.

## PREPARATIONS

**Oral:** 500mg tablets.
Liquid (as a manufactured 'special' - unlicensed medicine).
Rifater tablets (rifampicin 120mg, isoniazid 50mg, pyrazinamide 300mg).
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).

**Paediatric oral fixed dose combinations (dissolvable in water):**

| Weight | Number of tablets | |
|---|---|---|
| | **Intensive phase RHZ 75/50/150 *** | **Continuation phase RH 75/50** |
| 4-7 kg | 1 | 1 |
| 8-11 kg | 2 | 2 |
| 12-15 kg | 3 | 3 |
| 16-24 kg | 4 | 4 |
| ≥25kg | Adult dose recommended | Adult dose recommended |

***Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.*

## DRUG LEVEL MONITORING

**Indications for monitoring:**
- Known or suspected malabsorption.
- Poor treatment response.

**Target Level:** 20 – 40mg/L *(Peak).*
**Timing of sample:**
- 2 hours post dose.
- Repeat at 6 hours if suspect delayed**.**

**Frequency of Levels:**
- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Hyperuricaemia.**
**Arthralgia.**
**Gastrointestinal**: Anorexia, nausea, vomiting.
**Hepatic:** Transient increases in LFTs.
**Dermatological:** Rash.
**SERIOUS:**
**Haematological**: Sideroblastic anaemia (rare), thrombocytopaenia (rare).
**Hepatotoxity.**

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

Probenecid: Pyrazinamide antagonises the effect of probenecid.
Sulfinpyrazone: Pyrazinamide antagonises the effect of sulfinpyrazone.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To pyrazinamide.
**Cautions:**
**Gout.**
**Liver Disease.**

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
**Sample Type**: Serum.
**Volume Required**: 2 ml.
**Sample Container**: Plain (non SST).
**Container Type**: Any.
**Availability**: Office Hours.
**Turnaround Time**: 7 Days.

# RIFABUTIN

## DOSAGE

**Adult:** 5mg/kg once a day (oral). Usual dose is 300mg, although doses of up to 450mg are sometimes used.
**Children:** 5mg/kg once a day (limited data).

## PREPARATIONS

**Oral:** 150mg capsules.

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Known or suspected malabsorption.
- Poor treatment response.

**Target Level:** 0.3 – 0.9mg/L *(Peak)*
**Timing of sample:**

- 3 hours post dose.
- Repeat at 7 hours if suspect delayed**.**

**Frequency of Levels:**

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
Reddish discolouration of urine, sweat, sputum, tears.
**Haematological:** Neutropaenia.
**Gastrointestinal**: Anorexia, nausea, vomiting, heartburn.
**Hepatic**: Transient increases in LFTs.
**Opthalmic:** Uveitis.
**Dermatological:** Rash.
**SERIOUS:**
**Haematological**: Anaemia, neutropaenia, thrombocytopaenia.

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

**Anti-arrhythmics:** Accelerated metabolism of disopyramide.
**Anticoagulants:** Accelerated metabolism of coumarins (e.g. warfarin).
**Anti-diabetics:** Accelerated metabolism of tolbutamide and sulfonylureas (reduced effect).
**Antiepileptics:** Reduced plasma concentration of carbamazepine and phenytoin.
**Antifungals**: increased serum concentration of rifabutin with fluconazole, posaconazole, and voriconazole, and possibly itraconazole. Reduced serum concentrations of itraconazole, posaconazole and voriconazole. If benefit outweighs the risk, monitor antifungal serum

concentrations (increase dose of voriconazole); and monitor for rifabutin adverse effects such as leukopaenia and uveitis.
**Antipsychotics:** Possible reduced plasma concentration of aripiprazole.
**Antivirals**: *Please seek advice from an HIV physician before considering starting rifampicin in patients on anti-retrovirals due to the frequency of drug interactions:* Increased serum concentration of rifabutin when given with: amprenavir, Fosamprenavir/ritonavir, Lopinavir/ritonavir, Ritonavir, and Tipranavir/ritonavir. Reduce dose of rifabutin. Consider alternative protease inhibitor to ritonavir.
**Atovaquone:** Reduced plasma concentrations of both rifabutin and atovaquone.
**Contraceptives**: Accelerated metabolism of oestrogens and progestogens (reduced contraceptive effect).
**Corticosteroids:** Possible accelerated metabolism of corticosteroids (reduced effect).
**Hormone Replacement Therapy (HRT):** Rifampicin would be expected to reduce the efficacy of HRT
**Macrolides:** Increased risk of neutropaenia with azithromycin; increased plasma concentration of rifabutin when taken with clarithromycin and possibly erythromycin (reduce dose of rifabutin).
**P-aminosalicylic acid**: Reduced absorption of rifamycins. Give 8-12 hours apart.
**Sirolimus:** Reduced in plasma concentration of sirolimus.
**Tacrolimus:** Reduced in plasma concentration of tacrolimus.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To rifabutin or other rifamycins.
**Pregnancy.**
**Breast-feeding.**
**Cautions:**
**Liver Disease:** Use cautiously and monitor LFTs.
**Renal Disease:** Reduce dose in severe renal impairment.

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
**Sample Type**: Serum.
**Volume Required**: 2 ml.
**Sample Container**: Plain (non SST).
**Container Type**: Any.
**Availability**: Office Hours.
**Turnaround Time**: 7 Days.

# RIFAMPICIN

## DOSAGE

**Adults (<50kg):** 450mg once a day (oral or intravenous); **or** for DOT supervised regimen: 600mg three times a week (oral).
**Adults (50kg+):** 600mg once a day (oral or intravenous); **or** for DOT supervised regimen: 900mg three times a week (oral).
**Children:** 15mg/kg (max. 450mg if <50kg; 600mg if 50kg+) once a day (oral or intravenous); **or** for DOT supervised regimen: 15mg/kg (max. 900mg) three times a week (oral). (*Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of capsule*).

Rifampicin should be taken 30-60 minutes before food, or 2 hours after food.

## PREPARATIONS

**Oral:** 150mg, 300mg capsules.
100mg/5mL syrup.
Rifinah® 300/150 tablets (rifampicin 300mg, isoniazid 150mg).
Rifinah® 150/100 tablets (rifampicin 150mg, isoniazid 100mg).
Rifater tablets (rifampicin 120mg, isoniazid 50mg, pyrazinamide 300mg).
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).

**Paediatric oral fixed dose combinations (dissolvable in water):**

| Weight | Number of tablets | |
|---|---|---|
| | **Intensive phase RHZ 75/50/150 *** | **Continuation phase RH 75/50** |
| 4-7 kg | 1 | 1 |
| 8-11 kg | 2 | 2 |
| 12-15 kg | 3 | 3 |
| 16-24 kg | 4 | 4 |
| ≥25kg | Adult dose recommended | Adult dose recommended |

***Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.*

**Parenteral:** 600mg powder for reconstitution.

## DRUG LEVEL MONITORING

**Indications for monitoring:**
- Known or suspected malabsorption.
- Poor treatment response.

**Target Level:** 8 – 24mg/L *(Peak).*
**Timing of sample:**
- 2 hours post dose.

- Repeat at 6 hours if suspect delayed.

**Frequency of Levels:**

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**

Reddish discolouration of urine, sweat, sputum, tears.
**Gastrointestinal**: Anorexia, nausea, vomiting, heartburn.
**Hepatic:** Transient increases in LFTs.
Flu-like syndrome.

**SERIOUS:**

**Haematological:** Agranulocytosis (rare), Haemolytic anaemia (rare, usually intermittent therapy), Thrombocytopaenia (rare, usually high-dose / intermittent therapy).
**Hepatic:** Hepatotoxicity (rare).
**Renal:** Nephrotoxicity (rare).

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

**Analgesics:** Accelerated metabolism of opiates, resulting in reduced effect (e.g. alfentanyl, codeine, fentanyl, methadone, morphine and possibly oxycodone).
**Antacids:** Reduced absorption of rifampicin.
**Anti-arrhythmics:** Accelerated metabolism of disopyramide.
**Antibacterials:** Reduced plasma concentrations of chloramphenicol, clarithromycin, dapsone, doxycycline, linezolid, trimethoprim.
**Anticoagulants:** Reduced plasma concentration of apixaban, dabigatran and rivaroxaban; accelerated metabolism of coumarins (e.g. warfarin).
**Anti-diabetics:** Accelerated metabolism of tolbutamide and sulfonylureas (reduced effect); reduced effect of linagliptan, netaglinide and repaglinide.
**Antiepileptics:** Reduced plasma concentration of lamotrigine and phenytoin; phenobarbital possibly reduces plasma concentration of rifampicin.
**Antifungals**: Accelerated metabolism of ketoconazole, fluconazole, itraconazole, posaconazole, terbinafine and voriconazole (reduced plasma concentrations; avoid concomitant use of rifampicin with itraconazole or voriconazole). Rifampicin initially increases then decreases caspofungin levels (consider increasing caspofungin dose).
**Antimalarials:** Reduced plasma concentration of mefloquine (avoid use) and quinine.
**Antipsychotics:** Accelerated metabolism of haloperidol and possibly aripiprazole and clozapine.
**Antivirals**: Reduced plasma concentration of atazanavir, darunavir, fosamprenavir, lopinavir, nelfinavir, nevirapine, rilpivirine, saquinavir and telaprevir (avoid concomitant use), and possibly abacavir, boceprevir, ritonavir, and tipranavir. Rifampicin also reduces plasma concentration of efavirenz (increase dose of efavirenz), maraviroc and raltegravir (consider increasing doses). Accelerated metabolism of indinavir (avoid concomitant use).
**Atovaquone:** Reduced plasma concentrations of atovaquone; increased plasma concentration of rifampicin (avoid concomitant use).
**Bosentan:** Reduced plasma concentration of bosentan (avoid concomitant use).

**Calcium-channel blockers:** Accelerated metabolism of diltiazem, nifedipine, nimodipine and verapamil (significant reduction in plasma concentrations), and possibly isradipine and nicardipine.
**Ciclosporin:** Accelerated metabolism of ciclosporin (reduced plasma concentration.
**Contraceptives**: Accelerated metabolism of oestrogens and progestogens (reduced contraceptive effect). Avoid use of combined hormonal contraception (oral, patch or vaginal ring), progestogen-only contraception (pill and implant). Suitable alternatives include barrier methods, copper-bearing intrauterine system, or progestogen-only injectable (depot medroxyprogesterone acetate, norethisterone enantate, or levonorgestrel-releasing intrauterine system, which can be continued at the usual dose and dosing/replacement interval of 12 weeks, 8 weeks and 5 years, respectively).
**Corticosteroids:** Accelerated metabolism of corticosteroids (reduced effect).
**CFTR modulators:** reduced plasma concentration of ivacaftor, tezacaftor, elexacaftor
**Diuretics:** Reduced plasma concentration of eplerenone (avoid concomitant use).
**Hormone Replacement Therapy (HRT):** Rifampicin would be expected to reduce the efficacy of HRT.
**Mycophenolate:** Reduced plasma concentration of active metabolite of mycophenolate.
**P-aminosalicylic acid**: Reduced absorption of rifamycins. Give 8-12 hours apart.
**Ranolazine:** Reduced plasma concentration of ranolazine (avoid concomitant use).
**Sirolimus:** Reduced in plasma concentration of sirolimus.
**Tacrolimus:** Reduced in plasma concentration of tacrolimus.
**Tadalafil:** Reduced plasma concentration of tadalafil (avoid concomitant use).
**Theophylline:** Accelerated metabolism of theophylline (reduced plasma concentration).
**Ticagrelor:** Reduced plasma concentration of ticagrelor.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To rifampicin or other rifamycins.
**Liver Disease:** Avoid if jaundiced.
**Drug Interactions:** Avoid concomitant use with saquinavir or ritonavir.
**Cautions:**
**Liver Disease:** Use cautiously and monitor LFTs; hyperbilirubinaemia may occur early in treatment in some patients due to competition between rifampicin and bilirubin for hepatic excretion.

## LABORATORY INFORMATION

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**Sample Type**: Serum.
**Volume Required**: Please note that rifampicin binds to glass and plastics and therefore there may be a significant loss of drug if a small volume of serum is dispatched in a relatively large container. Please try and fill the container to 2/3 -3/4 its capacity).
**Sample Container**: Plain glass or plastic (non SST).
**Container Type**: Any.
**Availability**: Office Hours.
**Turnaround Time**: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.
**Please telephone at least one day in advance of the sample.**



The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

# RIFAPENTINE

*Please note rifapentine is not licensed in the UK, and currently is not recommended by NICE.*

## DOSAGE – Active Tuberculosis

***MANUFACTURER RECOMMENDATIONS***
**Adults, and children over 12 years:**

- **Intensive phase (maximum 2 months):** 600mg twice weekly with an interval of no less than 72 hours (3 days).
    - **NB. The American Thoracic Society, US Centers for Disease Control and Prevention, and Infectious Diseases Society of America currently do not recommend use of rifapentine during the initial intensive phase of tuberculosis treatment.**
- **Continuation phase:** 600mg once weekly.

**Children under 12 years:** 0-12 years: Rifapentine is not recommended.

**NB. HIGHER DOSES HAVE BEEN STUDIED, e.g. in the RIFAQUIN Trial.**
**Adults, and children over 12 years:**

- **Intensive phase (maximum 2 months):** daily rifampicin, pyrazinamide, ethambutol and moxifloxacin. (NB. Rifapentine was not used in the intensive phase).
- **Continuation phase: Rifapentine** 1200mg (8 x 150mg tablets) once a week for four months (in combination with moxifloxacin 400mg once a week).

## DOSAGE - Latent Tuberculosis Infection

**Adults:** 900 mg once weekly for 12 doses (in combination with isoniazid 15mg/kg (maximum 900mg) once a week).
**Children: (12 years and older):** Once weekly dose for 12 weeks based on weight (in combination with isoniazid 15mg/kg (maximum 900mg) once a week):

- 10.0‑14.0 kg = 300 mg once weekly.
- 14.1‑25.0 kg = 450 mg once weekly.
- 25.1‑32.0 kg = 600 mg once weekly.
- 32.1‑49.9 kg = 750 mg once weekly.
- >50 kg = 900 mg once weekly.

*Rifapentine should be taken with meals to maximise absorption, especially for people with active tuberculosis.*
***NB:** In people with latent tuberculosis infection, taking rifapentine with meals may be difficult because isoniazid should be taken on an empty stomach. For this indication, we recommend that rifapentine and isoniazid are taken at the same time on an empty stomach, or with a light snack if nauseated.*

## PREPARATIONS

**Oral:** 150mg oral tablets

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
Reddish discolouration of urine, sweat, sputum, tears.
Flu-like syndrome.
**Gastrointestinal**: Anorexia, nausea, vomiting, heartburn.
**Hepatic:** Transient increases in LFTs.
**Metabolic:** Hypoglycaemia, hyeruricaemia
**SERIOUS:**
**Haematological:** Agranulocytosis (rare), Haemolytic anaemia (rare, usually intermittent therapy), Thrombocytopaenia (rare, usually high-dose / intermittent therapy).
**Hepatic:** Hepatotoxicity (rare), Hyperbilirubinaemia.
**Renal:** Nephrotoxicity (rare).
**Immunologic:** Hypersensitivity.

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTONS

**Analgesics:** Accelerated metabolism of opiates, resulting in reduced effect (e.g. alfentanyl, codeine, fentanyl, methadone, morphine and possibly oxycodone).
**Anti-arrhythmics:** Accelerated metabolism of disopyramide.
**Antibacterials:** Reduced plasma concentrations of chloramphenicol, clarithromycin, dapsone, doxycycline and fluoroquinolones.
**Anticoagulants:** Accelerated metabolism of coumarins (e.g. warfarin).
**Anti-diabetics:** Accelerated metabolism of sulfonylureas (reduced effect).
**Antiepileptics:** Reduced plasma concentration of antiepileptics such as phenytoin.
**Antifungals**: Reduced serum concentrations of fluconazole, itraconazole and ketoconazole. If benefit outweighs the risk, monitor antifungal serum concentrations.
**Antipsychotics:** Accelerated metabolism of antipsychotics such as haloperidol.
**Antivirals**: *Please seek advice from an HIV physician before considering starting rifapentine in patients on anti-retrovirals due to the frequency of drug interactions:* reduced serum concentration of certain reverse transcriptase inhibitors (e.g., delavirdine, zidovudine).
**Atovaquone:** Reduced plasma concentrations of both rifapentine and atovaquone.
**Benzodiazpeines:** Reduced plasma concentrations (e.g. diazepam).
**Betablockers:** Reduced effect of betablockers; dosage adjustment maybe required.
**Calcium-channel blockers:** Accelerated metabolism of diltiazem, nifedipine, and verapamil (significant reduction in plasma concentrations).
**Ciclosporin:** Accelerated metabolism of ciclosporin (reduced plasma concentration).
**Contraceptives**: Accelerated metabolism of oestrogens and progestogens (reduced contraceptive effect). Avoid use of combined hormonal contraception (oral, patch or vaginal ring), or progestogen-only contraception (pill and implant). Suitable alternatives include barrier methods, copper-bearing

intrauterine system, or progestogen-only injectable (depot medroxyprogesterone acetate, norethisterone enantate, or levonorgestrel-releasing intrauterine system, which can be continued at the usual dose and dosing/replacement interval of 12 weeks, 8 weeks and 5 years, respectively).
**Corticosteroids:** Possible accelerated metabolism of corticosteroids (reduced effect).
**Hormone Replacement Therapy (HRT):** Rifapentine would be expected to reduce the efficacy of HRT
**Levothyroxine:** Reduced effect of levothyroxine; dosage adjustment maybe required.
**Sildenafil:** Reduced plasma concentration of sildenafil.
**Sirolimus:** Potential for reduction in plasma concentration of sirolimus.
**Tacrolimus:** Reduced in plasma concentration of tacrolimus.
**Theophylline:** Accelerated metabolism of theophylline (reduced plasma concentration).
**Tri-cyclic antidepressants:** Reduced effect of tri-cyclic antidepressants; dosage adjustment maybe required.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** To rifapentine or other rifamycins.
**Liver Disease:** Avoid if jaundiced.
**Drug Interactions:** Avoid concomitant use with saquinavir or ritonavir.
**Cautions:**
**Liver Disease:** Use cautiously and monitor LFTs; hyperbilirubinaemia may occur early in treatment in some patients due to competition between rifampicin and bilirubin for hepatic excretion.
**Pregnancy.**
**Breast feeding.**

## LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.

# STREPTOMYCIN

*Please note streptomycin is not licensed in the UK.*
Streptomycin is not usually recommended for the treatment of MDRTB, as half of UK cases are resistant to streptomycin.

## PREPARATIONS

**Parenteral:** 1g powder for reconstitution for injection (unlicensed medicine).

## DOSAGE

**For intramuscular administration only**. There is experience of using streptomycin as an intravenous infusion, but the prescriber should ensure the streptomycin preparation used is suitable for intravenous administration.
Streptomycin is usually given once daily for an initial period (usually at least two months), then the frequency may be reduced to three times weekly.

**Adults: 15mg/kg daily** (usual maximum 1g daily, but can be increased if necessary in large muscular adults). After initial period: **15mg/kg three times per week**.
**Age >59 years: 10mg/kg daily** (maximum 750mg daily). After initial period: **15mg/kg three times per week**.

**Renal failure: 12-15mg/kg** TWO to THREE times a week. *Please discuss with a pharmacist.*

**Obesity:** It has been suggested that markedly obese patients should have an adjusted dose using ideal body weight plus 40% of the excess weight in markedly obese patients. The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.

- Male ideal body weight (kg) = 50 + (2.3 x height in cm above (152.4/2.54))
- Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above (152.4/2.54))

Adjust dose and/or frequency according to serum streptomycin concentration (see below).

**Children:** 20-40mg/kg daily (maximum 1g daily). After initial period: 20-40mg/kg three times per week.
Adjust dose and/or frequency according to serum streptomycin concentration (see below).

## DRUG LEVEL MONITORING

**Indications for monitoring:**

- Ensure therapeutic dose
- Ensure renal clearance, especially in at risk patients (e.g. renal impairment, elderly)

**Target Level:** <5mg/L (*trough*)
25 – 35mg/L (*peak)*
**Timing of sample:**

- Pre dose
- 60mins after infusion ends

**Frequency of Levels:**


The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

- Peak serum level in first week, repeat if poor response.
- Trough serum levels weekly for 4 weeks, fortnightly for 4 weeks, then monthly if stable

## ADVERSE EFFECTS

**COMMON:**
**Nephrotoxicity:** Accumulation if renal impairment.
**Ototoxicity:** Irreversible vestibulocochlear nerve damage.
**Hypersensitivity skin reactions:** Rashes, urticaria, erythroderma.
**Drug-induced eosinophillia** (Usually subsides with intermittent dosing).
**SERIOUS:**
**Endocrine:** Hypocalcaemia, hypomagnesaemia, and hypokalaemia
**Immunological:** Anaphylaxis (uncommon).
**Neurological:** Neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually dose-related and self-limiting).
**Audiological:** Ototoxicity - auditory > vestibular (higher with prolonged use and older age).
**Renal:** Nephrotoxicity (higher with prolonged use).

## ADVERSE EFFECTS: MONITORING

**Renal**, **auditory** and **vestibular** monitoring is essential

**Renal function**: Month 1 = twice weekly
Month 2 = weekly
Month 3: End of treatment with an aminoglycoside = 2 weekly
Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable.
Consider increasing frequency of monitoring if evidence of renal impairment.

**Loss of hearing** usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances including tinnitus are also signs of **ototoxicity**.
*Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies. If this occurs, Amikacin should be discontinued or dosing reduced in frequency to avoid further hearing loss, although the hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change. Of the current injectable agents, Capreomycin may be less ototoxic.*

We recommend that patients have baseline audiometry and then monthly reviews until treatment with aminoglycoside ceases. A final audiometry review should be offered 2 months after the final dose.
Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTIONS

Increased risk of **nephrotoxicity** if given with: capreomycin, cephalosporins, ciclosporin, colistimethate sodium, tacrolimus
Increased risk of **ototoxicity** if given with: loop diuretics
Increased risk of **hypocalcaemia** with bisphosphonates.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**Hypersensitivity:** to streptomycin or other aminoglycosides
**Myasthenia Gravis:** as aminoglycosides may impair neuromuscular transmission
**Pregnancy:** Risk of vestibular or auditory nerve damage to infant if used in second or third trimester

**Cautions:**
**Obese:** Use ideal weight for height to calculate dose and monitor serum streptomycin levels closely
**Elderly:** Nephrotoxicity and ototoxicity common in the elderly; monitor and reduce dose if necessary
**Renal Disease:** Use with caution. Reduce the frequency of dosing and monitor serum concentrations.

## LABORATORY INFORMATION

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**Sample Type**: Serum.
**Volume Required**: 2ml (min 0.1mL).
**Sample Container**: Plain glass or plastic (non SST).
**Container Type**: Any.
**Availability**: Office Hours.
**Turnaround Time**: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.

# TERIZIDONE

*Please note terizidone is not licensed for the treatment of tuberculosis in the UK*.
It may be sourced from the specialist importer 'Clinigen'.

## DOSAGE

Terizidone is a structural analog that is a combination of two cycloserine molecules. It is thought to undergo hydrolysis of imine groups in terizidone to cycloserine and para-phthalate.

Please note: Cycloserine and terizidone are considered interchangeable (equivalent). The longer half-life of terizidone would make it more suitable for once daily dosing than cycloserine, although there is much less PK/PD data on terizidone.

**Adults:** Initially 250mg to 500mg per day (oral in one or two divided doses), increased to 1000mg per day (in two divided doses, or once a day if tolerated) depending on cycloserine serum concentrations.
The usual target dose in adults is 10-20mg/kg/day, given in two divided doses (or once a day if tolerated). Maximum 1g per day.

Avoid high-fat meals at the time of taking terizidone.

**Children:** 15-20 mg/kg once daily. Maximum 1g per day.

*All patients must be prescribed pyridoxine whilst receiving terizidone. The usual dose ranges from 50 to 100mg daily, up to 50mg per 250mg of terizidone.*

**Renal failure:**
Reduce dose if creatinine clearance < 30 ml/min, to 250mg once daily or intermittently 500mg on three days per week (for example Monday, Wednesday and Friday).
Dialysis patients should take terizidone after dialysis sessions. There are insufficient data to determine whether terizidone is clinically effective in people undergoing continuous forms of dialysis (e.g. continuous peritoneal dialysis).

## PREPARATIONS

**Oral:** 250mg capusules.

## DRUG LEVEL MONITORING

**Indications for drug level monitoring:**

- Ensure therapeutic dose.
- Ensure toxic levels are not reached.
- Renal impairment.
- If patients are switched to terizidone from cycloserine

**Target Level of cycloserine:** 20 – 35mg/L (peak)
10 – 20mg/L

**Timing of sample:**

- Peak: 2 hours post dose.
- Repeat at 6 hours if suspect delayed absorption.
- Trough levels – taken immediately prior to a dose.

**Frequency of Levels:**

- Serum levels after 7 days at target dose.
- Repeat fortnightly for one month and until stable. Serum levels may increase over a 2-week period despite a stable dose due to accumulation of cycloserine.
- Repeat at least 6 monthly.
- Repeat if suspect malabsorption, treatment failure, or neuropsychiatric side effects (should be monitored monthly).
- Patients with reduced renal function require more frequent monitoring, initially weekly until stable.

**Suggested Actions:**

- **High Peak Level:** Reduce dose if level >35mg/L. If level is 35 to 50mg/L, consider reducing dose by 25% per day. If level >50mg/L, consider halving the dose. Recheck level after four days.
- **Low Peak Level:** Increase dose if level <15mg/L.
- **Trough levels:** Terizidone/Cycloserine absorption may be slow and consequently a 2-hour peak level may not capture the true Cmax. It is rare to see elevated peak levels in the absence of elevated trough levels, therefore a raised trough level may indicate potentially toxic 'true' peak levels. Consider serial peak serum level assays (e.g. at 2, 4 and 6 hours post dose), and dose reduction

## ADVERSE EFFECTS

**COMMON:**

**Neurological:** Confusion, disorientation, dizziness, somnolence (increased risk if peak serum level >35mg/L).

**SERIOUS:**

**Cardiovascular:** Cardiac arrhythmias, and sudden development of congestive heart failure (rarely reported at doses greater than 1 to 1.5g daily).

**Dermatological:** Rash and photosensitivity, Stevens-Johnson syndrome (rare).

**Haematological:** Vitamin B12 and/ or folic acid deficiency, megaloblastic anaemia or sideroblastic anaemia (rare).

**Psychiatric:** Depression, seizure, psychotic disturbances (increased risk if peak serum level >35mg/L).

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTIONS

Alcohol: Increased risk of convulsions with terizidone.

Isoniazid: Increased risk of CNS toxicity when given with terizidone.

High fat meals: Delayed and reduced absorption of terizidone.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**

**Hypersensitivity:** To cycloserine or terizidone.

**Neurological:** Epilepsy, depression, severe anxiety, psychotic states. Alcohol Dependence.

**Renal Disease:** Severe renal impairment.

**Cautions:**

**Pregnancy & Breast-feeding**

**Neurological:** Stop or reduce dose if symptoms of central nervous system toxicity such as convulsions, psychosis, somnolence, depression, confusion, hyper-reflexia, headache, tremor, vertigo, paresis or dysarthria.

**Dermatological:** Stop or reduce dose if allergic dermatitis develops.

**Renal Disease:** Use with caution. Reduce dose in severe renal impairment.

## LABORATORY INFORMATION

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# THIOACETAZONE

*Please note thioacetazone is not licensed for the treatment of tuberculosis in the UK*.
Thioacetazone is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

## DOSAGE

**Adults:** 150mg once daily.
**Children:** No information.

## PREPARATIONS

**Not currently available in the UK.**

## DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

## ADVERSE EFFECTS

**COMMON:**
**Dermatological:** Rash (3%).
**Gastrointestinal:** Nausea, vomiting, diarrhoea, anorexia & dyspepsia.
**Neurological**: Giddiness (10%).
**SERIOUS:**
**Haematological**: Neutropaenia, anaemia, thrombocytopaenia; rarely: haemolytic anaemia, agranulocytosis, aplastic anaemia.
**Hepatic**: Hepatotoxicity with jaundice and acute hepatic failure.
**Neurological**: Dizziness, peripheral neuropathy, cerebral oedema (rare).

## ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

## INTERACTIONS

Streptomycin: Possible increased ototoxicty.

*This information is not inclusive of all drug interactions. Please discuss with a pharmacist.*

## CONTRA-INDICATIONS & CAUTIONS

**Contraindications:**
**HIV co-infection:** Causes fatal skin rashes.
**Prothionamide resistance:** Risk of cross-resistance

NB: Thioacetazone is poorly tolerated by people of Asian or European origin. It is surprisingly well tolerated in East African countries and in South America. Consequently Thioacetazone is not routinely used by any of the TB programs we know in Cambodia, Lao PDR, Vietnam and China. Even

in people of African or South American ethnicity, its use should be avoided in patients with HIV co-infection.

## LABORATORY INFORMATION

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The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment https://www.who.int/publications/i/item/9789240007048 and the BTS MDR-TB Clinical Advisory Service https://www.brit-thoracic.org.uk/quality-improvement/lung-disease-registries/bts-mdr-tb-clinical-advice-service/

## BIBLIOGRAPHY


Alffenaar, J.-W. C. et al. (2010) 'Comparison of the pharmacokinetics of two dosage regimens of linezolid in multidrug-resistant and extensively drug-resistant tuberculosis patients.', Clinical pharmacokinetics, 49(8), pp. 559–65. doi: 10.2165/11532080-000000000-00000.

Alliance, G. et al. (2017) 'Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children', WHO, (December 2015), pp. 0–1.

Alsultan, A. and Peloquin, C. A. (2014) 'Therapeutic drug monitoring in the treatment of tuberculosis: an update.', Drugs, 74(8), pp. 839–54. doi: 10.1007/s40265-014-0222-8.

Anon (1968) 'A controlled comparison of thiacetazone (thioacetazone) plus isoniazid with PAS plus isoniazid in Hong Kong.', Tubercle, 49(3), pp. 243–80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4179210 (Accessed: 4 September 2013).

Anon (2008a) 'Amikacin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 87–8. doi: 10.1016/S1472-9792(08)70003-9.

Anon (2008b) 'Capreomycin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 89–91. doi: 10.1016/S1472-9792(08)70004-0.

Anon (2008c) 'Clarithromycin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 92–5. doi: 10.1016/S1472-9792(08)70005-2.

Anon (2008d) 'Clofazimine.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 96–9. doi: 10.1016/S1472-9792(08)70006-4.

Anon (2008e) 'Cycloserine.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 100–1. doi: 10.1016/S1472-9792(08)70007-6.

Anon (2008f) 'Ethambutol.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 102–5. doi: 10.1016/S1472-9792(08)70008-8.

Anon (2008g) 'Isoniazid.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 112–6. doi: 10.1016/S1472-9792(08)70011-8.

Anon (2008h) 'Levofloxacin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 119–21. doi: 10.1016/S1472-9792(08)70013-1.

Anon (2008i) 'Linezolid.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 122–5. doi: 10.1016/S1472-9792(08)70014-3.

Anon (2008j) 'Moxifloxacin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 127–31. doi: 10.1016/S1472-9792(08)70016-7.

Anon (2008k) 'Para-aminosalicylic acid.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 137–8. doi: 10.1016/S1472-9792(08)70019-2.

Anon (2008l) 'Prothionamide.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 139–40. doi: 10.1016/S1472-9792(08)70020-9.

Anon (2008m) 'Pyrazinamide.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 141–4. doi: 10.1016/S1472-9792(08)70021-0.

Anon (2008n) 'Rifabutin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 145–7. doi: 10.1016/S1472-9792(08)70022-2.

Anon (2008o) 'Rifampin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 151–4. doi: 10.1016/S1472-9792(08)70024-6.

Anon (2008p) 'Rifapentine.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 155–8. doi: 10.1016/S1472-9792(08)70025-8.

Anon (2008q) 'Streptomycin.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 162–3. doi: 10.1016/S1472-9792(08)70027-1.

Anon (2008r) 'TMC-207.', Tuberculosis (Edinburgh, Scotland), 88(2), pp. 168–9. doi: 10.1016/S1472-9792(08)70029-5.

Ashley, C and Currie, A. (ed.) (2009) The Renal Drug Handbook. 3rd edn. Radcliffe Medical Press, Oxford.

ASHP (2011) AHFS Drug Information, American Society of Health-System Pharmacists, Bathesda, USA.

Auclair, B. et al. (2001) 'Pharmacokinetics of Ethionamide Administered under Fasting Conditions or with Orange Juice, Food, or Antacids', Antimicrobial agents and chemotherapy, 45, pp. 810–4. doi: 10.1128/AAC.45.3.810.

Aventis (2003) 'Priftin® (rifapentine) tablets prescribing information (dated Feb 2002).', in Montvale, N. (ed.) Physicians' desk reference 5th edition. 5th edn. Medical Economics Company Inc, pp. 763–6.

Banerjee, S., Narayanan, M. and Gould, K. (2012) 'Monitoring aminoglycoside level.', BMJ (Clinical research ed.), 345, p. e6354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23044986 (Accessed: 24 August 2013).

Black, H. R., Griffith, R. S. and Peabody, A. M. (1966) 'Absorption, excretion and metabolism of capreomycin in normal and diseased states.', Annals of the New York Academy of Sciences, 135(2), pp. 974–82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/5220250 (Accessed: 19 August 2013).

Boeree, M. J. et al. (2015) 'A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis', American Journal of Respiratory and Critical Care Medicine, 191(9), pp. 1058–1065. doi: 10.1164/rccm.201407-1264OC.

Boeree, M. J. et al. (2016) 'High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial', The Lancet Infectious Diseases. The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY license, 3099(16), pp. 1–11. doi: 10.1016/S1473-3099(16)30274-2.

Bolhuis, M. S. et al. (2010) 'Clarithromycin significantly increases linezolid serum concentrations.', Antimicrobial agents and chemotherapy, 54(12), pp. 5418–9. doi: 10.1128/AAC.00757-10.

Bolhuis, M. S. et al. (2013) 'Clarithromycin increases linezolid exposure in multidrug-resistant tuberculosis patients.', The European respiratory journal, 42(6), pp. 1614–21. doi: 10.1183/09031936.00001913.

British National Formulary (2013). The British Medical Association and the Royal Pharmaceutical Society. Available at: www.bnf.org.

British National Formulary For Children (2013). British Medical Association, Royal Pharmaceutical Society, Royal College of Paediatrics and Child Health, and Neonatal and Paediatric Pharmacists Group. Available at: www.bnfc.org.

Cabrera-rivero, J. L. et al. (2012) 'new england journal', pp. 2151–2160.

Caminero, J. A. (2013) 'Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis 2013', International Union Against Tuberculosis And Lung Disease. International Union Against Tuberculosis And Lung Disease.

Chambers, H. F. et al. (2005) 'Imipenem for treatment of tuberculosis in mice and humans.', Antimicrobial agents and chemotherapy, 49(7), pp. 2816–21. doi: 10.1128/AAC.49.7.2816-2821.2005.

Chan, S. L. et al. (1994) 'Comparison of Chinese and Western rifapentines and improvement of bioavailability by prior taking of various meals', International Journal of Antimicrobial Agents, 3(4), pp. 267–274. doi: 10.1016/0924-8579(94)90054-X.

Chaulet, P., Raviglione, M. and Bustreo, F. (1996) 'Epidemiology, control and treatment of multidrug-resistant tuberculosis.', Drugs, 52 Suppl 2, pp. 103–7; discussion 107-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8869846 (Accessed: 19 August 2013).

Choudhri, S. H. et al. (1995) 'Clofazimine induced cardiotoxicity--a case report.', Leprosy review, 66(1), pp. 63–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7731343 (Accessed: 6 November 2013).

Conradie, F. et al. (2022) 'Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis', New England Journal of Medicine. Massachusetts Medical Society, 387(9), pp. 810–823. doi: 10.1056/NEJMoa2119430.

Court, R. et al. (2018) 'Steady state pharmacokinetics of cycloserine in patients on terizidone for multidrug-resistant tuberculosis', The International Journal of Tuberculosis and Lung Disease, 22(1), pp. 30–33. doi: 10.5588/ijtld.17.0475.

Cox, H. and Ford, N. (2012) 'Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 16(4), pp. 447–54. doi: 10.5588/ijtld.11.0451.

Curry International Tuberculosis Center (2022) Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. 3rd edn.

Dannemann, B. et al. (2012) 'QTcF prolongation in a Phase II trial of TMC207 plus background regimen as treatment for multidrug-resistant tuberculosis: effect of co-administration with clofazimine', 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy.

Dauby, N. et al. (2011) 'Meropenem/clavulanate and linezolid treatment for extensively drug-resistant tuberculosis.', The Pediatric infectious disease journal, 30(9), pp. 812–3. doi: 10.1097/INF.0b013e3182154b05.

Devine, B. (1974) 'Gentamicin therapy', Drug Intell Clin Pharm, 8, pp. 650–655.

Dey, T. et al. (2013) 'Outcomes of clofazimine for the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis.', The Journal of antimicrobial chemotherapy, 68(2), pp. 284–93. doi: 10.1093/jac/dks389.

Diacon, A. H. et al. (2009) 'The diarylquinoline TMC207 for multidrug-resistant tuberculosis.', The New England journal of medicine, 360(23), pp. 2397–405. doi: 10.1056/NEJMoa0808427.

Diacon, Andreas H et al. (2012) '14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial.', Lancet, 380(9846), pp. 986–93. doi: 10.1016/S0140-6736(12)61080-0.

Diacon, A H et al. (2012) 'Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance.', Antimicrobial agents and chemotherapy, 56(6), pp. 3271–6. doi: 10.1128/AAC.06126-11.

Diacon, A. H. et al. (2014) 'Multidrug-resistant tuberculosis and culture conversion with bedaquiline.', The New England journal of medicine, 371(8), pp. 723–32. doi: 10.1056/NEJMoa1313865.

Donald, P. R. et al. (2001) 'Early bactericidal activity of amoxicillin in combination with clavulanic acid in patients with sputum smear-positive pulmonary tuberculosis.', Scandinavian journal of infectious

diseases, 33(6), pp. 466–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11450868 (Accessed: 24 August 2013).

Durrant JD, Campbell K, F. S. et al (2009) Ototoxicity Monitoring, American Academy of Audiology. Available at: http://www.audiology.org/resources/documentlibrary/Documents/OtoMonGuidelines.pdf.

Dutta, B. S. et al. (2012) 'Ethionamide-induced hypothyroidism.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 16(1), p. 141. doi: 10.5588/ijtld.11.0388.

Falzon, D. et al. (2011) 'WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update.', The European respiratory journal, 38(3), pp. 516–28. doi: 10.1183/09031936.00073611.

Garcia-Prats, AJ Donald, PR Hesseling, AC Schaaf, H. (2013) 'Second-Line Antituberculosis Drugs in Children: A Commissioned Review for the World Health Organization 19th Expert Committee on the Selection and Use of Essential Medicines', World Health Organisation. Available at: www.who.int/selection_medicines/committees/expert/19/applications/TB_624_C_R.pdf.

Goh, T. L. et al. (2011) 'Extensively drug-resistant tuberculosis: New Zealand's first case and the challenges of management in a low-prevalence country.', The Medical journal of Australia, 194(11), pp. 602–4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21644877 (Accessed: 24 August 2013).

Gonzalo, X. and Drobniewski, F. (2013) 'Is there a place for β-lactams in the treatment of multidrug-resistant/extensively drug-resistant tuberculosis? Synergy between meropenem and amoxicillin/clavulanate.', The Journal of antimicrobial chemotherapy, 68(2), pp. 366–9. doi: 10.1093/jac/dks395.

Gordin, F. et al. (2011) 'new england journal', pp. 2155–2166.

Gynaecology, R. C. of O. and (2011) Drug Interactions with Hormonal Contraception. Faculty of Sexual & Reproductive Healthcare Clinical Guidance. Available at: http://www.fsrh.org/pdfs/CEUguidancedruginteractionshormonal.pdf.

Hasenbosch, R. E. et al. (2008) 'Ethambutol-induced optical neuropathy: risk of overdosing in obese subjects.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 12(8), pp. 967–71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18647459 (Accessed: 21 February 2017).

Hoc, A. et al. (1994) 'Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy'. doi: 10.1044/policy.GL1994-00003.

Hutchison TA, S. D. & A. M. (no date) Drugdex System Internet version Micromedex Inc. Greenwood Village, Colorado.

Im, J. H. et al. (2015) 'Incidence and risk factors of linezolid-induced lactic acidosis', International Journal of Infectious Diseases, 31, pp. 47–52. doi: 10.1016/j.ijid.2014.12.009.

Janssen (2012a) 'Anti-Infective Drugs Advisory Committee Meeting Briefing Document: TMC207 (bedaquiline): Treatment of Patients with MDR-TB', NDA, pp. 204–384.

Janssen (2012b) 'Compassionate Use Program of TMC207 in Patients with Extensively Drug Resistant (XDR) or Pre-XDR Mycobacterium tuberculosis (MTB) Pulmonary Infection', Guidelines for physicians and pharmacists.

Janssen (2012c) SirturoTM U.S. Food and Drug Administration bedaquiline package insert. Available at: http://www.who.int/tb/challenges/mdr/bedaquiline/en/index.html.

Jindani, A. et al. (2014) 'High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis', New England Journal of Medicine, 371(17), pp. 1599–1608. doi: 10.1056/NEJMoa1314210.

Katiyar, S. K. et al. (2008) 'A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 12(2), pp. 139–45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18230245 (Accessed: 4 September 2013).

Lee, M. et al. (2012) 'Linezolid for treatment of chronic extensively drug-resistant tuberculosis.', The New England journal of medicine, 367(16), pp. 1508–18. doi: 10.1056/NEJMoa1201964.

Lee, M. et al. (2015) 'Linezolid for XDR-TB — Final Study Outcomes', New England Journal of Medicine, 373(3), pp. 290–291. doi: 10.1056/NEJMc1500286.

Lehmann, C. R. et al. (1988) 'Capreomycin kinetics in renal impairment and clearance by hemodialysis.', The American review of respiratory disease, 138(5), pp. 1312–3. doi: 10.1164/ajrccm/138.5.1312.

Loeffler, A. et al (2011) Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. 2nd edn. Curry International Tuberculosis Center and California Department of Public Health.

De Lorenzo, S. et al. (2013) 'Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB.', The European respiratory journal, 41(6), pp. 1386–92. doi: 10.1183/09031936.00124312.

Migliori, G. B. et al. (2009) 'A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis.', The European respiratory journal, 34(2), pp. 387–93. doi: 10.1183/09031936.00009509.

Milburn, H. et al. (2010) 'Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease.', Thorax, 65(6), pp. 557–70. doi: 10.1136/thx.2009.133173.

Mulubwa, M. and Mugabo, P. (2019) 'Amount of Cycloserine Emanating from Terizidone Metabolism and Relationship with Hepatic Function in Patients with Drug-Resistant Tuberculosis', Drugs in R&D, 19(3), pp. 289–296. doi: 10.1007/s40268-019-00281-4.

Mylan IRE Healthcare Limited (2022) Summary of Product Characteristics: Dovprela®., Electronic Medicines Compendium: Datapharm Communications Ltd. Available at: http://emc.medicines.org.uk.

National Collaborating Centre for Chronic Conditions (UK); Centre for Clinical Practice at NICE (UK (2011) Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and Control.

Nyang'wa, B.-T. et al. (2022) 'A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis', New England Journal of Medicine. Massachusetts Medical Society, 387(25), pp. 2331–2343. doi: 10.1056/NEJMoa2117166.

Organisation, W. H. (2012) 'Interim guidance on the use of bedaquiline to treat MDR-TB', World Health Organisation, p. WHO/HTM/TB/2013.6.

Payen, M. C. et al. (2012) 'Clinical use of the meropenem-clavulanate combination for extensively drug-resistant tuberculosis.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 16(4), pp. 558–60. doi: 10.5588/ijtld.11.0414.

Peloquin, C. A. (1993) 'Pharmacology of the antimycobacterial drugs.', The Medical clinics of North America, 77(6), pp. 1253–62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8231410 (Accessed: 19 August 2013).

Peloquin, C. A. et al. (1999) 'Once-daily and twice-daily dosing of p-aminosalicylic acid granules.', American journal of respiratory and critical care medicine, 159(3), pp. 932–4. doi: 10.1164/ajrccm.159.3.9807131.

Peloquin, C. A. (2002) 'Therapeutic drug monitoring in the treatment of tuberculosis.', Drugs, 62(15), pp. 2169–83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12381217 (Accessed: 4 September 2013).

Peloquin, C. A. et al. (2004) 'Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases.', Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 38(11), pp. 1538–44. doi: 10.1086/420742.

PfizerTrecator® (2007) U.S. Physician Prescribing Information, PfizerTrecator®. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=473 (Accessed: 28 August 2013).

Pharmaceuticals, K. (no date) 'Personal communication: Capreomycin and intravenous administration.'

Pranger, A. D. et al. (2011) 'Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience.', The European respiratory journal, 38(4), pp. 888–94. doi: 10.1183/09031936.00176610.

Prasad, R. et al. (no date) 'Efficacy and safety of kanamycin, ethionamide, PAS and cycloserine in multidrug-resistant pulmonary tuberculosis patients.', The Indian journal of chest diseases & allied sciences, 48(3), pp. 183–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18610675 (Accessed: 24 August 2013).

Rose, P. C. et al. (2012) 'Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 16(12), pp. 1588–93. doi: 10.5588/ijtld.12.0322.

Ruslami, R. et al. (2013) 'Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial.', The Lancet infectious diseases, 13(1), pp. 27–35. doi: 10.1016/S1473-3099(12)70264-5.

Rustomjee, R. et al. (2008) 'Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis.', Antimicrobial agents and chemotherapy, 52(8), pp. 2831–5. doi: 10.1128/AAC.01204-07.

Schaaf, H. S. and Marais, B. J. (2011) 'Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians.', Paediatric respiratory reviews, 12(1), pp. 31–8. doi: 10.1016/j.prrv.2010.09.010.

Schilling, R. (2013) 'Appropriate monitoring for prolonged QT', Unpublished communication.

Seddon, J. a et al. (2012) 'Caring for children with drug-resistant tuberculosis: practice-based recommendations.', American journal of respiratory and critical care medicine, 186(10), pp. 953–64. doi: 10.1164/rccm.201206-1001CI.

Skripconoka, V. et al. (2013) 'Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis.', The European respiratory journal, 41(6), pp. 1393–400. doi: 10.1183/09031936.00125812.

Sotgiu, G. et al. (2012) 'Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis.', The European respiratory journal, 40(6), pp. 1430–42. doi: 10.1183/09031936.00022912.

Sotgiu, G. et al. (2016) 'Carbapenems to Treat Multidrug and Extensively Drug-Resistant Tuberculosis: A Systematic Review', International Journal of Molecular Sciences, 17(3), p. 373. doi: 10.3390/ijms17030373.

Soumakis, S. A., Berg, D. and Harris, H. W. (1998) 'Hypothyroidism in a Patient Receiving Treatment for Multidrug-Resistant Tuberculosis', Clinical Infectious Diseases, 27(4), pp. 910–911. doi: 10.1086/517171.

Srivastava, S. et al. (2013) 'Therapeutic drug management: is it the future of multidrug-resistant tuberculosis treatment?', The European respiratory journal, 42(6), pp. 1449–53. doi: 10.1183/09031936.00073213.

STOP TB Partnership, Child Health Subgroup, World Health Organisation, Geneva, S. (2010) 'Rapid advice: Treatment of Tuberculosis in Children', WHO, p. WHO/HTM/TB/2010.13.

STOP TB Partnership Child Health Subgroup, W. H. O. (2006) 'Guidance for national tuberculosis programmes on the management of tuberculosis in children. Chapter 2: anti-tuberculosis treatment in children.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 10(11), pp. 1205–11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17131777 (Accessed: 4 September 2013).

Sturdy, A. et al. (2011) 'Multidrug-resistant tuberculosis (MDR-TB) treatment in the UK: a study of injectable use and toxicity in practice.', The Journal of antimicrobial chemotherapy, 66(8), pp. 1815–20. doi: 10.1093/jac/dkr221.

Sweetman S, M. (ed.) (no date) The Complete Drug Reference, online edition., The Pharmaceutical Press, London. The Pharmaceutical Press, London.

Tang, S. et al. (2015) 'Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China.', The European respiratory journal, 45(1), pp. 161–70. doi: 10.1183/09031936.00035114.

The Sentinel Project for Pediatric Drug-Resistant Tuberculosis (2015) 'Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide', (March). Available at: http://sentinel-project.org/wp-content/uploads/2015/03/Field_Handbook_2nd_Ed_revised-no-logos_03022015.pdf.

Thee, S., Zöllner, E. W., et al. (2011) 'Abnormal thyroid function tests in children on ethionamide treatment.', The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 15(9), pp. 1191–3, i. doi: 10.5588/ijtld.10.0707.

Thee, S., Seifart, H. I., et al. (2011) 'Pharmacokinetics of ethionamide in children.', Antimicrobial agents and chemotherapy, 55(10), pp. 4594–600. doi: 10.1128/AAC.00379-11.

Tiberi, S. et al. (2016) 'Ertapenem in the treatment of multidrug-resistant tuberculosis: first clinical experience: TABLE 1', European Respiratory Journal, 47(1), pp. 333–336. doi: 10.1183/13993003.01278-2015.

Treatment of Tuberculosis: Thioacetazone (no date) People's Friendship University of Russia, Faculty of Medicine. Available at: http://main.rudn.ru/_new/russian/win/tub1/tubeng2012/05_treat/05_1_7_treat_tiacet.htm.

Tucker, H. (2005) Dear Healthcare Professional Letter. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164879.pdf.

WHO (2004) Statement on the position of the stop TB department with regard to thioacetazone + isoniazid within context of the who model list of essential medicines., World Health Organisation. Available at:

http://archives.who.int/eml/expcom/expcom14/thioacetazone/thioacetazoneisoniazid_STB_statement_annex_4Nov04.pdf.

WHO (2006) 'Guidance for National Tuberculosis Programmes on the management of tuberculosis in children', World Health Organisation. Geneva, p. WHO/HTM/ TB/2006.371, WHO/FCH/CAH/2006.7.

WHO (2009) 'Treatment of Tuberculosis: guidelines 4th edition.', WHO, p. WHO/HTM/TB/2009.4.

WHO (2011) 'Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 Update', World Health Organisation, p. WHO/HTM/TB/2008.402.

WHO (2013) 'The Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance.', Geneva: World Health Organization. Available at: http://www.ncbi.nlm.nih.gov/books/NBK154134/.

WHO (2014a) Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis., World Health Organisation. Geneva, Switzerland: World Health Organisation. Available at: http://www.who.int/tb/publications/pmdt_companionhandbook/en/.

WHO (2014b) 'The use of delamanid in the treatment of multidrug-resistant tuberculosis: An interim policy guidance.', World Health Organisation. Geneva, Switzerland, (WHO/HTM/TB/2014.23). Available at: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf?ua=1&ua=1.

WHO (2015) Guidelines on the management of latent tuberculosis infection. Geneva, Switzerland. Available at: http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf?ua=1&ua=1.

WHO (2022a) 'Use of delamanid in children and adolescents with multidrug-and rifampicin-resistant tuberculosis-Information note WHO recommendations for delamanid in children and adolescents', 4(6), pp. 1–8.

WHO (2022b) WHO consolidated guidelines on tuberculosis., WHO Press.

World Health Organization (2018) 'Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis.', p. 63. Available at: http://apps.who.int/bookorders. (Accessed: 26 April 2020).

World Health Organization (2023) 'Use of bedaquiline in children and adolescents with multidrug-and rifampicin-resistant tuberculosis-Information note BEDAQUILINE', 4(5), pp. 1–8. Available at: https://www.who.int/publications/i/item/9789240074286.

Xu, H.-B., Jiang, R.-H. and Xiao, H.-P. (2012) 'Clofazimine in the treatment of multidrug-resistant tuberculosis.', Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 18(11), pp. 1104–10. doi: 10.1111/j.1469-0691.2011.03716.x.

Zhang, X. et al. (2015) 'Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis.', Journal of thoracic disease, 7(4), pp. 603–15. doi: 10.3978/j.issn.2072-1439.2015.03.10.

Zhu, M. et al. (2001) 'Population pharmacokinetics of intravenous and intramuscular streptomycin in patients with tuberculosis.', Pharmacotherapy, 21(9), pp. 1037–45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11560193 (Accessed: 4 September 2013).

Zhu, M. et al. (2002) 'Population pharmacokinetics of ethionamide in patients with tuberculosis.', Tuberculosis (Edinburgh, Scotland), 82(2–3), pp. 91–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12356460 (Accessed: 26 April 2014).