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

1st Published May 2014
Latest update: June 2017

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With thanks to:

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7 Barts Health NHS Trust, Department of Cardiology, London United Kingdom
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9 The Pennine Acute Hospitals NHS Trust, North Manchester Hospital, Department of Pharmacy, Manchester, United Kingdom
### Abbreviations

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

WHO guidance on the treatment of MDR-TB:
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## Baseline and generic tests for adverse effects monitoring in patients being treated for MDR-TB

### ONGOING MONITORING RECOMMENDATIONS

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<th>Recommendation</th>
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<td><strong>FBC</strong></td>
<td>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.</td>
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<td><strong>Clotting</strong></td>
<td>Baseline and repeat if indicated, particularly if deranged LFTs.</td>
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| **U&Es**              | All MDR patients should be on an aminoglycoside therefore:  
                        | - Month 1 = twice weekly  
                        | - Month 2 = weekly  
                        | - Month 3 onwards: 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. |
| **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. |
| **Calcium**           | Monthly until 6 months. Consider reducing frequency after 6 months if stable and no changes to medication. |
| **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. |
| **ECG**               | Baseline, at 2 weeks, then 3 monthly (1 monthly if on bedaquiline or delamanid) throughout treatment.  
                        | Repeat if symptomatic or after the addition of any new medication which is known to prolong QT.  
                        | Be particularly cautious when prescribing more than one drug which might prolong QTc such as ondansetron, anti-depressants, anti-psychotics etc.  
                        | If on more than one drug which prolongs QTc we recommend monthly monitoring once stable.  
                        | Increase monitoring to 2 weekly if QTc outside the normal range (>470 in women, >450 in men).  
                        | Stop offending medication if QTc greater than 500 and refer to EP cardiologist. |
| **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.  
                        | 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** (Aminoglycosides) | Monthly until completion of treatment and a final test 2 months after treatment completion. |
DRUG MONOGRAPHS
AMIKACIN

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

DOSEAGE

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:** 15-22.5mg/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.
- 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 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 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.
BEDAQUILINE

There are limited data available on bedaquiline. Clinicians are advised to monitor patients closely to ensure the safe and effective use of this drug.

Patients should be advised that the following serious side effects can occur with bedaquiline: death, heart rhythm abnormalities, and/or hepatitis. In addition, patients should also be advised about other potential side effects: nausea, joint pain, headache, increased blood amylase, haemoptysis, chest pain, anorexia, and/or rash. Additional testing may be needed to monitor or reduce the likelihood of adverse effects.

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: not currently recommended in people aged less than 18 years.

Bedaquiline should be taken with food.

Patients should be advised to avoid alcohol whilst on bedaquiline.

PREPARATIONS

Oral: 100mg 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:
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:

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 treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.
Drug Monographs for Medicines used in the Treatment of Multi-Drug Resistant Tuberculosis

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 treatment guideline [http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) and the BTS MDR-TB Clinical Advisory Service [http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx](http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx).

- 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.

**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:**

**Pregnancy & breast feeding.** Men should agree to use a highly effective method of birth control and not to donate sperm during treatment and for 3 months after receiving the last dose of TB treatment.

*There are no adequate or well-controlled studies in pregnant women. It is not known whether bedaquiline or its metabolites are excreted in human milk.*

**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.

**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](http://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.
Drug Monographs for Medicines used in the Treatment of Multi-Drug Resistant Tuberculosis

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 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 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.

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 treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.
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 maraviro, 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

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.
CLOFAZIMINE

Please note clofazimine is not licensed for the treatment of tuberculosis in the UK. Clofazimine 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:** 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:** Limited data, WHO recommendation is based on experience and expert opinion and suggests 1mg/kg/day.

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 discoloration.

**Other:** Splenic infarction, discoloration 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 bedaquiline.

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.
**CO-AMOXICLAV**

*Please note co-amoxiclav is not licensed for the treatment of tuberculosis in the UK.*

Co-amoxiclav 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. It is sometimes recommended in combination with meropenem for its clavulanate content. Co-amoxiclav inhibits the beta-lactamase which destroys meropenem activity. Clavulanate alone is not available for use in the UK.

**DOSAGE**

[NOTE: Limited data on evidence for dosing in TB. The adult doses are based on those used in the treatment of respiratory tract infections in the BNF no 65, March 2013. The paediatric doses are similarly based on dosing for respiratory tract infections in the latest BNF for children 2012-13].

*For all patients over 12 years old:*

**By intravenous infusion over 3-4 minutes:**
- **Patients over 12 years old:** 1.2g 8 hourly
- **Neonates:** 30mg/kg every 12 hours
- **Children 1 -3 months** 30mg/kg every 12 hours
- **3 months – 18 years** 30mg/kg every 8 hours

**By mouth:**
- **Patients over 12 years old:** 625mg, 8 hourly
- **Neonates:** 0.25 mL/kg of 125/31 suspension every 8 hours
- **Children 1 month- 1 year:** 0.25 mL/kg of 125/31 suspension every 8 hours
  - Dose doubled in severe infection
- **1–6 years:** 5 mL of 125/31 suspension every 8 hours
  - or 0.25 mL/kg of 125/31 suspension every 8 hours
  - Dose doubled in severe infection
- **6–12 years:** 5 mL of 250/62 suspension every 8 hours
  - or 0.15 mL/kg of 250/62 suspension every 8 hours
  - Dose doubled in severe infection

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

**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%).
Drug Monographs for Medicines used in the Treatment of Multi-Drug Resistant Tuberculosis

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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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 treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.
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:** Target dose is 10-20mg/kg/day in two divided doses. 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 – 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 4 days at target dose.
- Repeat fortnightly for one month and until stable.
- 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:** 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

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 treatment guideline [http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) and the BTS MDR-TB Clinical Advisory Service [http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx](http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx).
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.

INTERACTIONS
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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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 treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.
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:** Not currently recommended in people aged less than 18 years.

**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 MDR TB. 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:**

- **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, thrombocytopenia, leucopenia.
- **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:
Drug Monographs for Medicines used in the Treatment of Multi-Drug Resistant Tuberculosis

- 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.*

**INTERACTIONS**

*Many of the drugs listed below increase the risk of prolonged QT interval when used in combination with Delamanid. 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 bradycardias, 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**

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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): 20mg/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

Ophthalmic:
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 Ophthalmic 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.**

INTERACTIONS

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:** 20-40mg/kg (max 2g) three times a day (intravenous).  
  
Note: Meropenem is preferred in children.

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%), eosinophilia (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:** Pancytopenia, neutropenia, leucopenia, thrombocytopenia, 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.
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):**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Number of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive phase RHZ 75/50/150</td>
</tr>
<tr>
<td>4-7 kg</td>
<td>1</td>
</tr>
<tr>
<td>8-11 kg</td>
<td>2</td>
</tr>
<tr>
<td>12-15 kg</td>
<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
</tr>
<tr>
<td>≥25 kg</td>
<td>Adult dose recommended</td>
</tr>
</tbody>
</table>

*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: 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, thrombocytopenia.
Hepatic: Hepatotoxicity (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 hepatotoxicity.
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

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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 fluoroquinolone 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 (>5 years):** 10-15mg/kg once daily.
**Children (<5 years):** 7.5-10mg/kg twice a day (limited experience).

**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).
- Haematological: Eosinophilia, leucopaenia (uncommon), thrombocytopenia, neutropaenia (rare).
- Hepatic: Acute hepatitis (rare).
- Immunological: Anaphylaxis, immune hypersensitivity (uncommon).
- Musculoskeletal: Tendon inflammation and rupture (see contra-indications below).

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 treatment guideline [http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) and the BTS MDR-TB Clinical Advisory Service [http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx](http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx).
**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.
- 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](http://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.**
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 ≤11 years:** 10mg/kg three times daily

**Children >11 years:** 10mg/kg twice 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: Weekly for the first 4 months. 2 weekly between 4 and 6 months. Consider reducing to monthly if stable thereafter.
NOTE: Some papers suggest using a lower dose of 300mg may be better tolerated in terms of myelosuppression.

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, SHT₁ 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, phaeochromocytoma, 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–12 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: Thrombocytopenia.
Hepatic: Transient increases in LFTs.
Neurological: Headache (2-8%).

SERIOUS:
Dermatological: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Haematological: Eosinophilia, thrombocytopenia, 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.

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 treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.
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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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.
- If using a fluoroquinolone we would recommend moxifloxacin as first choice agent followed by levofloxacin.

**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:** 7.5 – 10mg/kg once a day (oral).

**WHO**

**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.
Drug Monographs for Medicines used in the Treatment of Multi-Drug Resistant Tuberculosis

- **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).
  
  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, thrombocytopenia.
- **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](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf).

**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.

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 treatment guideline [http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) and the BTS MDR-TB Clinical Advisory Service [http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx](http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx).
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 tendonitis 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

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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:** 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.**
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 fluoroquinolone 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), thrombocytopenia, 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.
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).

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dose GranuPAS®/Paser®</th>
</tr>
</thead>
<tbody>
<tr>
<td>5kg</td>
<td>500mg twice daily</td>
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<tr>
<td>6-7kg</td>
<td>750mg twice daily</td>
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<tr>
<td>8-10kg</td>
<td>1000mg twice daily</td>
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<tr>
<td>11-14kg</td>
<td>1500mg twice daily</td>
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<tr>
<td>15-18kg</td>
<td>2000mg twice daily</td>
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<tr>
<td>19-22kg</td>
<td>2500mg twice daily</td>
</tr>
<tr>
<td>23-26kg</td>
<td>3000mg twice daily</td>
</tr>
<tr>
<td>27-30kg</td>
<td>3500mg twice daily</td>
</tr>
</tbody>
</table>

**Note:** P-aminosalicylic 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-aminosalicylic 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-aminosalicylic 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-aminosalicylic 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 thrombocytopenia.
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.

INTERACTIONS
Antacids: Fast dissolution of acid-resistant coating, resulting in early release of p-aminosalicylic acid into the stomach. However as the stomach gastric acid will have been neutralised, degradation of p-aminosalicylic acid to m-aminophenol will not occur. No dose adjustments required, however administration of p-aminosalicylic 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 hepatotoxicity.
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 1/70th 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.
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).

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 treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.
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 hepatotoxicity.
Rifampicin: increased risk of hepatotoxicity.

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
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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:** 35mg/kg (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):**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Number of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive phase</td>
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<tr>
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<td>12-15 kg</td>
<td>3</td>
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<tr>
<td>16-24 kg</td>
<td>4</td>
</tr>
<tr>
<td>≥25kg</td>
<td>Adult dose recommended</td>
</tr>
</tbody>
</table>

*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.

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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 treatment guideline [http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) and the BTS MDR-TB Clinical Advisory Service [http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx](http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx).
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 treatment guideline [http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) and the BTS MDR-TB Clinical Advisory Service [http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx](http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx).

**Gastrointestinal:** Anorexia, nausea, vomiting.

**Hepatic:** Transient increases in LFTs.

**Dermatological:** Rash.

**SERIOUS:**

**Haematological:** Sideroblastic anaemia (rare), thrombocytopenia (rare).

**Hepatotoxicity.**

**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**

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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.
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.
- Ophthalmic: Uveitis.
- Dermatological: Rash.

**SERIOUS:**
- Haematological: Anaemia, neutropaenia, thrombocytopaenia.

ADVERSE EFFECTS: MONITORING

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

INTERACTIONS

**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

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 treatment guideline [http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) and the BTS MDR-TB Clinical Advisory Service [http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx](http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx).
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**

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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.
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):

<table>
<thead>
<tr>
<th>Weight</th>
<th>Number of tablets</th>
</tr>
</thead>
<tbody>
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<td>Intensive phase RHZ 75/50/150</td>
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<tr>
<td>≥25kg</td>
<td>Adult dose recommended</td>
</tr>
</tbody>
</table>

*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 discoloration 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), Thrombocytopenia (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. alfentanil, 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 linagliptin, 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).

**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 plasma concentration of sirolimus.

**Tacrolimus:** Reduced plasma concentration of tacrolimus.

**Tadalafil:** Reduced plasma concentration of tadalafil (avoid concomitant use).

**Theophylline:** Accelerated metabolism of theophylline (reduced plasma concentration).

**Tacagrelor:** 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.
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, hyperuricaemia

SERIOUS:
Haematological: Agranulocytosis (rare), Haemolytic anaemia (rare, usually intermittent therapy), Thrombocytopenia (rare, typically high-dose / intermittent therapy).

Hepatic: Hepatotoxicity (rare), Hyperbilirubinemia.

Renal: Nephrotoxicity (rare).

Immunologic: Hypersensitivity.

ADVERSE EFFECTS: MONITORING
Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTIONS

Analgesics: Accelerated metabolism of opiates, resulting in reduced effect (e.g. alfentanil, 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 rifampicin 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.

Benzodiazepines: Reduced plasma concentrations (e.g. diazepam).

Beta-blockers: Reduced effect of beta-blockers; 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**

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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:
- 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 eosinophilia (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
- 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 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.

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.

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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.
THIOACETAZONE

Please note thiacetazone is not licensed for the treatment of tuberculosis in the UK.
Thiacetazone 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.

DOSEAGE
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, thrombocytopenia; 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 ototoxicity.

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: Thiacetazone is poorly tolerated by people of Asian or European origin. It is surprisingly well tolerated in East African countries and in South America. Consequently Thiacetazone 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 treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

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