NTM Network UK
Non-tuberculous mycobacteria

CONTENTS

NTM Network UK
Non-tuberculous mycobacteria

AMIKACIN – INTRAVENOUS

Please note AMIKACIN is not licensed for the treatment of NTM in the UK

DOSAGE

- **Adults**: 15mg/kg once daily (max 1g daily).
  - **Age >59 years:** 10mg/kg daily (maximum 750mg daily).
  - Thrice weekly dosing of 15-25mg/kg three times a week have been used.
- **Children**: Usually 15mg/kg once daily (max 1g daily). Dose should be based on ideal body weight.

- **Obesity** (where actual body weight (ABW) is >20% above ideal body weight (IBW)): it has been suggested that obese patients should have their dose adjusted based on an ideal body weight plus 40% of the excess weight (Adjusted body weight [AjBW]). The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.
  Male IBW (kg) = 50 + (0.91 x [height in cm - 152.4])
  Female IBW (kg) = 45.5 + (0.91 x [height in cm - 152.4])
  Adjusted body weight (AjBW) = IBW + (0.4 x [ABW-IBW])

- **Renal impairment**: dose reduction required; please discuss with a pharmacist

PATIENT COUNSELLING

- Signs of ototoxicity and vestibular toxicity: hearing loss, tinnitus, imbalance, dizziness, vertigo. Ototoxicity is usually irreversible if it were to occur, vestibular toxicity may resolve. NB. ototoxicity and vestibular toxicity can occur despite adequate level monitoring.
- Signs of nephrotoxicity: reduced urine output, ensure maintain adequate hydration.

PHARMACOKINETICS

- **Absorption:**
  - 100% bioavailability with intravenous administration.
- **Distribution:**
  - Diffuses readily through extracellular fluids. Distribution usually completed within 60 minutes of the infusion
  - Does not readily cross the blood-brain barrier
- **Metabolism:**
  - Not metabolised
- **Excretion:**
  - 94 - 98% of a single intravenous dose is excreted unchanged by glomerular filtration within 24 hours
- **Cmax:**
  - 35-45mg/L (calculated Cmax using linear regression to end of intravenous infusion)
  - 40-45mg/L at one hour after the end of the infusion
- **Tmax:**
  - One hour
- **Half-life:**
  - 2-3 hours in adults with normal renal function

Studies support a two-compartment model with first-order elimination to describe the pharmacokinetics of amikacin.

PREPARATIONS

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

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Ensure therapeutic dose
  - Ensure that accumulation is not occurring in renal impairment
- **Target Level:**
  - Trough (pre dose): <5mg/L
  - Peak (post dose): 40-45mg/L
- **Timing of Sample:**
  - Trough: immediately before a dose
  - Peak: 1 hour after the end of intravenous administration
- **Frequency of Levels:**
  - Peak serum levels in the first week, repeat if poor response
  - Trough serum levels minimum of weekly for 4 weeks; this can be reduced to fortnightly when stable.
- **Suggested actions:**
  - Pre-dose (trough) level: high - extend dosing interval
  - Peak level: high - reduce the dose; low - increase dose
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information
  - Cardiff and Vale University Health Board Medical Biochemistry and Immunology Department: https://cavuhb.nhs.wales/our-services/laboratory-medicine/medical-biochemistry-and-immunology/

ADVERSE EFFECTS

- **Common**
  - **Nephrotoxicity**: accumulation if renal impairment
  - **Ototoxicity and vestibular toxicity**: irreversible vestibulocochlear (eighth cranial) nerve damage leading to hearing loss, loss of balance, or both.
- **Serious**
  - **Audiological:** ototoxicity- auditory>vestibular toxicity (greater risk in patients with impaired renal function, older age, prolonged use and greater total cumulative dose)
  - **Endocrine:** hypocalcaemia, hypomagnesemia and hypokalaemia
  - **Neurological:** neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually dose-related and self-limiting).
  - **Renal:** nephrotoxicity (higher with prolonged use)

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- **Renal function**
  - Monitor twice weekly during month 1, weekly during month 2, then fortnightly during month 3 to the end of treatment. Consider increasing frequency of monitoring if there is evidence

of renal impairment.
- **Calcium, magnesium and potassium**
  - Repeat at least once a month.
- **Audiological and vestibular**
  - Loss of hearing usually occurs first and is detected by regular audiometric testing. High frequency hearing loss is seen most often. Vertigo, loss of balance and auditory disturbances including tinnitus are also signs of ototoxicity.
  - Ototoxicity on audiogram is defined as a 20dB loss from baseline at any one test frequency or a 10dB 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 hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change.
  - Patients should have baseline then monthly audiometry. Repeat until treatment with aminoglycoside ceases. A final audiometry review should be offered 2 months after the final dose.
- **Genetic testing (R.65 MT-RNR1 1555A>G)**
  - Where available and if your allocated regional commissioned NHS genomic labs have capacity, consider genetic testing for mitochondrial mutations, particularly the m.1555A>G mutation prior to starting treatment. MHRA safety review found an increased risk of deafness when using aminoglycosides in patients with mitochondrial mutations.
  - Mitochondrial mutations are rare (estimated prevalence is 0.2% in the general population) and the penetrance of the increased ototoxic effect is unknown.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Increased risk of **nephrotoxicity** if given with: capreomycin, cephalosporins, ciclosporin, colistimethate sodium, tacrolimus, nephrotoxic chemotherapy, non-steroidal anti-inflammatories, vancomycin (this can potentiate amikacin toxicity).
- **Bisphosphonates**: increased risk of hypocalcaemia.
- **Loop Diuretics**: increased risk of ototoxicity with loop diuretics.
- **Neuromuscular blocking drugs**: increased risk of neuromuscular blockade

- NB: There is no clinical benefit in prescribing amikacin AND capreomycin or kanamycin or streptomycin. Nebulised amikacin should also be avoided when intravenous aminoglycosides are considered.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Breastfeeding**: avoid use.
  - **Hypersensitivity** to amikacin or other aminoglycosides
  - **Hypersensitivity** to sulphite as injection contains sodium metabisulphate
  - **Ototoxicity or vestibular toxicity** from previous use of an aminoglycoside
  - **Myasthenia Gravis**: amikacin may impair neuromuscular transmission
  - **Pregnancy**: risk of vestibular or auditory nerve damage to foetus if used in second or third trimester

- **Cautions:**
  - **Obesity**: use adjusted body weight to calculate dose and monitor serum amikacin levels closely.
  - **Ototoxicity**: patients with known mitochondrial mutations (particularly the m.1555A>G mutation) which can be associated with an increased risk of ototoxicity.
  - **Elderly**: nephrotoxicity and ototoxicity common in elderly; monitor and reduce dose if necessary.
  - **Renal disease and renal transplant**: use with caution; reduce doses and monitor serum concentrations closely. Consult local guidance where available or consult the summary of product characteristics (SmPC), renal drug database or contact your specialist pharmacist where available.

NTM Network UK
Non-tuberculous mycobacteria

AMIKACIN – NEBULISED INJECTION

Please note AMIKACIN INJECTION is not licensed for the treatment of NTM in the UK.

DOSAGE

- **Adults**: 500mg twice daily (nebulised). In cases of intolerance after an initial initiation period, a dose reduction may be considered to 250–500mg once or twice daily (seek expert advice).
- **Children**: <12 years old: 250mg twice daily; ≥12 years old: 500mg twice daily.

- In the UK, the injectable preparation is given via the nebulised route, preferably using a suitable jet nebuliser with filter attachment (e.g. SideStream Plus with filter attachment, or Pari LC Plus). It is incompatible for use via the I-neb nebuliser machine and very slow via the eFlow device.
- The 250mg/mL injection vial should be used and made up to 4mLs with sodium chloride 0.9%. It must not be nebulised as a mixture with other nebulised drugs (e.g. salbutamol, dornase alfa, or other nebulised antibiotics).
- Suitable ancillaries such as needles and syringes must be provided and the patient/carer taught how to prepare each dose.

- **Renal impairment:** use with caution; avoid in severe renal impairment.

PATIENT COUNSELLING

- Signs of ototoxicity and vestibular toxicity: hearing loss, tinnitus, imbalance, dizziness, vertigo. Ototoxicity is usually irreversible if it were to occur, vestibular toxicity may resolve. NB. ototoxicity and vestibular toxicity can occur despite adequate level monitoring.
- Signs of nephrotoxicity: reduced urine output, ensure maintain adequate hydration.
- Patients with a history of reactive airways disease, asthma or bronchospasm should receive a short acting bronchodilator, e.g. salbutamol, prior to nebulised amikacin administration to reduce the risk of coughing and bronchospasm. This can be given nebulised or by their regular inhaler.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Highly variable. Median bioavailability 2.7%
- **Distribution:**
  - Expected to diffuse readily. Volume of distribution of 10.2L.
- **Metabolism:**
  - Not metabolised
- **Excretion:**
  - Excreted unchanged by glomerular filtration
- **Cmax:**
  - Peak serum concentrations of 8.2 - 9.2mg/L have been achieved when amikacin has been nebulised at doses of 40 to 60mg/kg.
- **Tmax:**
  - 2.2 (range 1.4 – 4.4) hours
- **Half-life:**
  - Median 1.6 (range 0.5 – 3.7) hours

Unlicensed route, limited data available

PREPARATIONS

- **Parenteral:** 500mg/2mL injection (preferred strength), 100mg/mL injection

DRUG LEVEL MONITORING

- **Indications for monitoring**:
  - Routine levels are not required
  - Ensure that accumulation is not occurring in renal impairment
- **Target Level**:
  - Trough (pre dose): <5mg/L
- **Timing of Sample**:
  - Trough: immediately before a dose
- **Frequency of Levels**:
  - Not routinely required. Repeat if concerns of potential for accumulation or toxicity.
- **Suggested Actions**:
  - Trough level: High - extend interval of dosing.
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information
  - Cardiff and Vale University Health Board Medical Biochemistry and Immunology Department: https://cavuhb.nhs.wales/our-services/laboratory-medicine/medical-biochemistry-and-immunology/

ADVERSE EFFECTS

Systemic adverse effects are less frequent when amikacin is given via the nebulised route, than via the intravenous route. However, respiratory adverse effects may be frequent especially in patients with underlying airways disease. Nebulised or an inhaled short acting beta-2 agonist pre-administration should be considered in patients who are at risk of bronchospasm.

- **Common**
  - **Gastrointestinal**: diarrhoea, nausea
  - **General**: fatigue
  - **Nephrotoxicity**: accumulation if renal impairment
  - **Ototoxicity and vestibular toxicity**: irreversible vestibulocochlear (eighth cranial) nerve damage leading to hearing loss, loss of balance, or both.
  - **Respiratory**: bronchospasm, dysphonia, sore throat, sore mouth, increased cough and wheeze, haemoptysis.
- **Rare but serious adverse effects**
  - **Immunological**: anaphylaxis & hypersensitivity reactions
  - **Neurological:** neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually dose-related and self-limiting).
  - **Ototoxicity:** ototoxicity- auditory>vestibular toxicity (greater risk in patients with impaired renal function, older age, prolonged use and greater total cumulative dose)
  - **Renal:** nephrotoxicity (higher with prolonged use)
  - **Respiratory**: allergic alveolitis and pneumonitis

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- **Renal function**
  - Monitor monthly during nebulised amikacin treatment.
- **Audiological and vestibular**
  - Loss of hearing usually occurs first and is detected by regular audiometric testing. High frequency hearing loss is seen most often. Vertigo, loss of balance and auditory disturbances including tinnitus are also signs of ototoxicity.
  - Ototoxicity on audiogram is defined as a 20dB loss from baseline at any one test frequency or a 10dB 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 hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change.
  - Patients should have baseline audiometry. This should be monitored periodically during treatment, with a final audiometry review offered 2 months after the final dose. Pragmatically, we recommend repeating every 2-3 months for most people, and monthly for people with known or suspected auditory or vestibular dysfunction, or as feasibly possible. Consider discussing capacity for audiometry testing with the local service.
- **Genetic testing (R.65 MT-RNR1 1555A>G) -**
  - Where available and if your allocated regional commissioned NHS genomic labs have capacity, consider genetic testing for mitochondrial mutations, particularly the m.1555A>G mutation prior to starting treatment. MHRA safety review found an increased risk of deafness when using aminoglycosides in patients with mitochondrial mutations.
  - Mitochondrial mutations are rare (estimated prevalence is 0.2% in the general population) and the penetrance of the increased ototoxic effect is unknown.
- **Respiratory**
  - Patients should have an initial supervised test dose with pre and post dose monitoring of lung function (spirometry).

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- There are no clinical drug interactions studies done with nebulised amikacin but pharmacodynamic interactions with drugs that increase the risk of neurotoxicity, nephrotoxicity and/or ototoxicity need to be considered.
- Increased risk of **nephrotoxicity** if given with: capreomycin, cephalosporins, ciclosporin, colistimethate sodium, tacrolimus, nephrotoxic chemotherapy, non-steroidal anti-inflammatories, vancomycin (this can potentiate amikacin toxicity).
- **Bisphosphonates**: increased risk of hypocalcaemia.
- **Loop Diuretics**: increased risk of ototoxicity with loop diuretics.
- **Neuromuscular blocking drugs**: increased risk of neuromuscular blockade

NB: There is no clinical benefit in prescribing amikacin AND capreomycin or kanamycin or streptomycin. Nebulised amikacin should also be avoided when intravenous aminoglycosides are prescribed.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to amikacin or other aminoglycosides
  - **Hypersensitivity** to sulphite as injection contains sodium metabisulphate
  - **Ototoxicity or vestibular toxicity** from previous use of an aminoglycoside
  - **Myasthenia Gravis**: amikacin may impair neuromuscular transmission
  - **Pregnancy**: risk of vestibular or auditory nerve damage to foetus if used in second or third trimester
- **Cautions:**
  - **Breastfeeding**: systemic exposure following inhalation is expected to be low compared to parenteral administration of amikacin. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inhaled liposomal amikacin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
  - **Ototoxicity**: patients with known mitochondrial mutations (particularly the m.1555A>G mutation) which can be associated with an increased risk of ototoxicity.
  - **Elderly**: nephrotoxicity and ototoxicity common in elderly; monitor and reduce dose if necessary.
  - **Renal disease and renal transplant**: use with caution (higher risk with intravenous administration). Consult local guidance where available or consult the summary of product characteristics (SmPC), renal drug database or contact your specialist pharmacist where available.

NTM Network UK
Non-tuberculous mycobacteria

NEBULISED LIPOSOMAL AMIKACIN (ARIKAYCE®)

Please note NEBULISED LIPOSOMAL AMIKACIN is only licensed for use in the UK, for the treatment of NTM lung infections caused by Mycobacterium Avium Complex in adults with limited treatment options who do not have cystic fibrosis.

DOSAGE

- **Adults**: 590mg nebulised once daily.
- **Children**: nebulised liposomal amikacin (Arikayce®) is not licensed for use in children. Safety and efficacy has not been established.

- **Renal impairment:** use with caution; contraindicated in severe renal impairment
- **Hepatic impairment:** no dose adjustment required in hepatic disease.
- No dose adjustment required in extremes of body weight. Consider therapeutic drug monitoring for underweight patients.

- The patient/carer must be taught how to prepare each dose. Inhaled liposomal amikacin must only be used with the Lamira Nebuliser System.
    - Liposomal amikacin must not be mixed with any other medical products

PATIENT COUNSELLING

- Nebuliser dispersion should be administered only using the Lamira Nebuliser System which is provided with the PARI eFlow system. A handset and 4 aerosol heads are supplied in each 28 day pack. The nebuliser controller is supplied separately.
- If a dose is missed, administer the usual dose the next day. Do not give a double dose.
- Store in a refrigerator (2 °C – 8 °C). Do not freeze. Arikayce can be stored at room temperature below 25 °C for up to 4 weeks.
- Signs of ototoxicity and vestibular toxicity: hearing loss, tinnitus, imbalance, dizziness, vertigo. Ototoxicity is usually irreversible if it were to occur, vestibular toxicity may resolve. NB. ototoxicity and vestibular toxicity can occur despite adequate level monitoring.
- Signs of nephrotoxicity: reduced urine output, ensure maintain adequate hydration.
- Patients with a history of reactive airways disease, asthma or bronchospasm should receive a short acting bronchodilator, e.g. salbutamol, prior to nebulised amikacin administration to reduce the risk of coughing and bronchospasm. This can be given nebulised or by their regular inhaler.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
    - Bioavailability: each 590mg dose delivers approximately 312mg amikacin
    - Systemic exposure of amikacin is low. Little to no accumulation occurs during daily treatment.
- **Distribution:**
    - ≤ 10% bound to serum proteins.
    - The mean total apparent volume of distribution has been estimated to be approximately 5.0 L/kg.
- **Metabolism:**

  - Not metabolised
- **Excretion:**
  - Excreted in the urine unchanged, primarily by glomerular filtration.
- **Cmax:**
  - Median serum Cmax 1.81 mg/L (range 0.482 – 6.87mg/L) at steady state
- **Tmax:**
  - 1 hour
- **Half-life:**
  - 3.29 – 14.0 hours

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PREPARATIONS

- **Nebulised:** 590mg nebuliser dispersion

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Routine levels are not required
  - Ensure that accumulation is not occurring in renal impairment
- **Target Level:**
  - Trough (pre dose): <5mg/L
- **Timing of Sample:**
  - Trough: immediately before a dose
- **Frequency of Levels:**
  - Not routinely required. Repeat if concerns of potential for accumulation or toxicity.
- **Suggested actions:**
  - Trough level: High - extend interval of dosing
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information
  - Cardiff and Vale University Health Board Medical Biochemistry and Immunology Department: https://cavuhb.nhs.wales/our-services/laboratory-medicine/medical-biochemistry-and-immunology/

ADVERSE EFFECTS

Systemic adverse effects are less frequent when amikacin is given via the nebulised route, than via the intravenous route. However, respiratory adverse effects may be more frequent.

- **Common**
  - **Gastrointestinal**: diarrhoea, nausea
  - **General**: fatigue
  - **Nephrotoxicity**: accumulation if renal impairment
  - **Ototoxicity and vestibular toxicity**: irreversible vestibulocochlear (eighth cranial) nerve damage leading to hearing loss, loss of balance, or both.
  - **Respiratory**: bronchospasm, dysphonia, sore throat, sore mouth, increased cough and wheeze, haemoptysis.
- **Serious**
  - **Immunological**: anaphylaxis and hypersensitivity reactions
  - **Neurological:** neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually dose-related and self-limiting).

- **Ototoxicity:** ototoxicity- auditory>vestibular toxicity (greater risk in patients with impaired renal function, older age, prolonged use and greater total cumulative dose)
- **Renal:** nephrotoxicity (higher with prolonged use)
- **Respiratory**: allergic alveolitis and pneumonitis

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- **Renal function**
  - Monitor monthly during nebulised amikacin treatment.
- **Audiological and vestibular**
  - Loss of hearing usually occurs first and is detected by regular audiometric testing. High frequency hearing loss is seen most often. Vertigo, loss of balance and auditory disturbances including tinnitus are also signs of ototoxicity.
  - Ototoxicity on audiogram is defined as a 20dB loss from baseline at any one test frequency or a 10dB 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 hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change.
  - Patients should have baseline audiometry. This should be monitored periodically during treatment, with a final audiometry review offered 2 months after the final dose. Pragmatically, we recommend repeating every 2-3 months for most people, and monthly for people with known or suspected auditory or vestibular dysfunction, or as feasibly possible. Consider discussing capacity for audiometry testing with the local service.
- **Genetic testing (R.65 MT-RNR1 1555A>G) -**
  - Where available and if your allocated regional commissioned NHS genomic labs have capacity, consider genetic testing for mitochondrial mutations, particularly the m.1555A>G mutation prior to starting treatment. MHRA safety review found an increased risk of deafness when using aminoglycosides in patients with mitochondrial mutations.
  - Mitochondrial mutations are rare (estimated prevalence is 0.2% in the general population) and the penetrance of the increased ototoxic effect is unknown.
- **Respiratory**
  - Patients should have an initial supervised test dose with pre and post dose monitoring of lung function.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- There are no clinical drug interactions studies done with nebulised amikacin but pharmacodynamic interactions with drugs that increase the risk of neurotoxicity, nephrotoxicity and/or ototoxicity need to be considered.
- Increased risk of **nephrotoxicity** if given with: capreomycin, cephalosporins, ciclosporin, colistimethate sodium, tacrolimus, nephrotoxic chemotherapy, non-steroidal anti-inflammatories, vancomycin (this can potentiate amikacin toxicity).
- **Bisphosphonates**: increased risk of hypocalcaemia.
- **Loop Diuretics**: increased risk of ototoxicity with loop diuretics.
- **Neuromuscular blocking drugs**: increased risk of neuromuscular blockade

NB: There is no clinical benefit in prescribing amikacin AND capreomycin or kanamycin or streptomycin. Nebulised amikacin should also be avoided when intravenous aminoglycosides are considered.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to amikacin or other aminoglycosides
  - **Hypersensitivity** to soya
  - **Ototoxicity or vestibular toxicity** from previous use of an aminoglycoside
  - **Myasthenia Gravis**: amikacin may impair neuromuscular transmission
  - **Pregnancy**: risk of vestibular or auditory nerve damage to foetus if used in second or third trimester
- **Cautions:**
  - **Breastfeeding**: systemic exposure following inhalation is expected to be low compared to parenteral administration of amikacin. The manufacturer recommends a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inhaled liposomal amikacin therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
  - **Ototoxicity**: patients with known mitochondrial mutations (particularly the m.1555A>G mutation) which can be associated with an increased risk of ototoxicity.
  - **Elderly**: nephrotoxicity and ototoxicity common in elderly; monitor and reduce dose if necessary.
  - **Renal disease and renal transplant**: use with caution (higher risk with intravenous administration). Consult local guidance where available or consult summary of product characteristics (SmPC), renal drug database or contact your specialist pharmacist where available.

AZITHROMYCIN

*Please note **AZITHROMYCIN** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults:** 250–500mg once daily (oral). In non-severe MAC-pulmonary disease, a dose of 500mg three times per week (oral) may be used.

Practice Point: the optimum dose has not been established. Dosing range reflects variation in practice determined by factors such as patient ideal body weight, potential interactions, co-morbidities and estimated mycobacterial load

- **Children:** Note: limited data on evidence for dosing in NTM. These doses are based on azithromycin dosing for respiratory tract infections in the latest BNF for children, September 2022 update

  - **Child 6 months–17 years**
    - 10mg/kg once daily (oral, max. per dose 500mg).
  - **Child 6 months–17 years (body-weight 15–25 kg)**
    - 200mg once daily (oral).
  - **Child 6 months–17 years (body-weight 26–35 kg)**
    - 300mg once daily (oral).
  - **Child 6 months–17 years (body-weight 36–45 kg)**
    - 400mg once daily (oral).
  - **Child 6 months–17 years (body-weight 46 kg and above)**
    - 500mg once daily (oral).

PATIENT COUNSELLING

- Can be taken with/without food
- Do not take indigestion remedies (or products which contain aluminium, magnesium, calcium or sodium salts or zinc 2 hours before or after you take this medicine)
- Common side effects include gastrointestinal upset (e.g. nausea (taking at night can help control this), vomiting, diarrhoea), tinnitus, hearing loss, hepatotoxicity or QTC prolongation

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Bioavailability is ~37%.
- **Distribution:**
  - Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 L/kg).
  - In serum the protein binding is variable and depending on the serum concentration varies from 50% in 0.05mg/L to 12% in 0.5mg/L.
  - Poorly penetrates the central nervous system (CNS).

- **Metabolism:**
  - Hepatic metabolism to inactive metabolites: N- and O- demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate
- **Excretion:**
  - The major route of elimination is via biliary excretion, predominantly in unchanged form
  - Approximately 12% of unchanged azithromycin is excreted in the urine.
- **Cmax:**
  - ~0.4mg/L (after a single oral dose of 500mg).
- **Tmax:**
  - 2-3 hours
- **Half-life:**
  - 2-4 days

PREPARATIONS

- **Oral:** 250mg and 500mg tablets, 250mg capsules, 200mg/5mL oral suspension

DRUG LEVEL MONITORING

- Drug levels cannot currently be performed in the UK

ADVERSE EFFECTS

- **Common**
  - **Dermatological**: rash, pruritus
  - **Gastrointestinal**: nausea, vomiting, diarrhoea, dyspepsia, change in taste, abdominal pain, flatulence
  - **General**: fatigue
  - **Metabolism**: anorexia
  - **Musculoskeletal and connective tissue**: arthralgia
  - **Neurological**: dizziness, headache, paraesthesia
  - **Ophthalmic**: visual impairment
  - **Ototoxicity**: deafness
  - **Cardiac QTc prolongation**

- **Serious**
  - **Blood and lymphatic system disorders**: leukopenia, neutropenia, eosinophilia, thrombocytopenia, haemolytic anaemia
  - **Dermatological**: acute generalised exanthematous pustulosis, Steven-Johnson syndrome, toxic epidermal necrolysis
  - **Gastrointestinal**: pancreatitis
  - **Hepatobiliary**: hepatitis, hepatic failure, hepatitis fulminant and hepatic necrosis
  - **Immunological**: angioedema, hypersensitivity, anaphylaxis
  - **Infections**: pseudomembranous colitis
  - **Neurological**: convulsion, myasthenia gravis
  - **Ototoxicity**: any change or loss in hearing including deafness, hearing impairment or tinnitus
  - **Renal and urinary disorders**: acute renal failure, interstitial nephritis

This information is not exhaustive. Please discuss with a pharmacist.

NTM Network UK
Non-tuberculous mycobacteria

ADVERSE EFFECTS: MONITORING

- LFTs, U&Es and FBC should be checked at baseline.
- LFTs should be repeated at least every 6 months.
- ECG: baseline, 4 weeks and after the addition of any new medication that is known to prolong QTc interval.
- **Calcium and magnesium**: at baseline and repeated if QT prolongation is detected.
- Ask about hearing loss, tinnitus and balance at every appointment. Consider baseline audiometry if there is a history of hearing difficulties, and repeat if patients report any hearing loss or tinnitus.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- **Amiodarone**: increased risk of QT prolongation
- **Antacids, or products which contain aluminium, magnesium, calcium or sodium salts or zinc**: reduced absorption; take 2 hours apart
- **Antiemetics**: increased risk of QT prolongation (e.g. domperidone, metoclopramide, 5HT3 antagonists)
- **Ciclosporin**: possible raised ciclosporin levels (monitor ciclosporin levels)
- **Colchicine**: possible increased colchicine levels and increased toxicity (monitor for nausea, vomiting, diarrhoea, myopathy and pancytopaenia)
- **Digoxin**: increased digoxin levels may occur (monitor digoxin levels)
- **Disopyramide**: increased risk of QT prolongation
- **Ergot derivatives**: ergotism has been precipitated by coadministration of some macrolide
- **Methadone:** possible increased risk of QT prolongation
- **Statins**: azithromycin is not usually expected to interact with statins due to lack of CYP3A4 inhibition, however case reports have been published
- **Tacrolimus**: case reports of raised tacrolimus concentrations (monitor tacrolimus levels)
- **Warfarin**: possible potentiated anticoagulation.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to azithromycin or any other macrolide
- **Cautions:**
  - **Audiological**: pre-existing hearing or balance disorders.
  - **Breastfeeding**
  - **Cardiac disease**: patients at risk of prolongation of QT interval
    - With congenital or documented QT prolongation.
    - Currently receiving treatment with other active substances known to prolong QT interval
    - With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
    - With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.
  - **Concomitant medicines**: patients receiving ergot derivatives

- **Liver disease**: patients with significant hepatic disease
- **Myasthenia gravis**
- **Pregnancy and breastfeeding**: limited data. Manufacturer advises that it may be considered for use if benefits to the mother outweigh potential risks to the child.
- **Renal disease**: severe renal impairment
- **Superinfections**: *Clostridium difficile* associated diarrhoea

BEDAQUILINE

*Please note **BEDAQUILINE** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults**: 400mg daily for the first 2 weeks, followed by 200mg three times per week*
- **Children**: (limited data in children for treating NTM. Doses based on recommendations for multidrug- and rifampicin-resistant tuberculosis):

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

*(at least 48 hours between doses)
Note that any treatment interruption of more than 28 days will require re-loading.

- **Hepatic impairment**: no dose adjustment in patients with mild or moderate hepatic impairment. Use with caution in patients with moderate hepatic impairment. Bedaquiline is not recommended in severe hepatic impairment.
- **Renal impairment:** no dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30mL/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis, bedaquiline should be used with caution. Bedaquiline is not removed by haemodialysis or peritoneal dialysis.

PATIENT COUNSELLING

- Bedaquiline should be taken with food (it helps optimise bioavailability).
- Avoid alcohol whilst on bedaquiline
- Tablets should be swallowed whole with water
    - For patients who have difficulty swallowing intact tablets, bedaquiline 20 mg tablets can be dispersed in water and administered. To aid with administration, the dispersed mixture in water can be further mixed with a beverage (e.g. water, milk product, apple juice, orange juice, cranberry juice or carbonated beverage) or soft food (e.g. yoghurt, apple sauce, mashed banana or porridge)
    - Bedaquiline 100mg tablets can also be crushed and swallowed with food.
- If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule
- If a dose is missed from week 3 onwards, patients should take the missed dose as soon as possible and then resume the three times a week regimen. The total dose of bedaquiline during a 7 day period should not exceed the recommended weekly dose (with at least 24 hours between each intake).
- Patients should be advised that if they experience a racing heartbeat or their heartbeat suddenly becomes more noticeable (palpitations), or if they faint, to contact their doctor or nurse immediately.
- If patients experience any nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light-coloured bowel movements, dark-coloured urine, yellowing of your skin or the white of your eyes, they should contact their doctor or nurse immediately.
- Bedaquiline may have a minor influence on the ability to drive and use machines. Dizziness has been reported in some patients taking bedaquiline.

PHARMACOKINETICS

- **Absorption:**
    - Bioavailability is increased by about 2-fold compared to administration under fasted conditions
- **Distribution:**
    - Highly protein bound (>99.9%)
    - No data on distribution into bone.
    - Undetectable levels in cerebrospinal fluid (CSF).
- **Metabolism:**
    - Bedaquiline is primarily metabolised in the liver by CYP3A4.
- **Excretion:**
    - Faeces is the major elimination route for bedaquiline
- **Cmax:**
    - 2.8 micrograms/mL at week 2 (at the end of the loading dose).
    - 1.3 micrograms/mL at week 24 (maintenance dose)
- **Tmax:**
    - 5 hours
- **Half-life:**
    - The effective half-life (describing the half-life associated with drug accumulation in plasma) is 24-30 hours.
    - The terminal elimination half-life of both bedaquiline and the active N-monodesmethyl metabolite (M2) is 2-8 months.
    - The long terminal half-life of bedaquiline does not drive short-term accumulation of bedaquiline in plasma, which is described by the effective half-life.

PREPARATIONS

- **Oral:** 100mg tablets
  20mg tablets (approved by the MHRA for use in the UK, but product not yet launched as of 2023)

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured

ADVERSE EFFECTS

Report all suspected adverse drug reactions to the Medicines and Healthcare Regulatory Authority

- **Common**
  - **Musculoskeletal and connective tissue disorders**: arthralgia, myalgia
  - **Cardiovascular**: QTc prolongation
  - **Gastrointestinal**: nausea, vomiting, diarrhoea
  - **Neurological**: headache, dizziness
  - **Respiratory**: haemoptysis

- **Serious**
  - **Cardiovascular**: QTc prolongation (more common in hypokalaemia, proarrhythmic conditions, in combination with other drugs that prolong the QTc interval especially drugs used for treatment of NTM such as clofazimine and azithromycin)
  - **Hepatic**: increases in LFTs

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- **ECG**:
  - Baseline, 2 weeks then every month and after the addition of any new medication that is known to prolong QTc. If QTc increases significantly above 480 ms monitor more frequently
  - Discontinue bedaquiline and all other QTc prolonging drugs if the patient develops:
    - Clinically significant ventricular arrhythmia
    - If patients develop significant cardiac symptoms such as palpitations which cannot be explained by other conditions.
    - A QTc interval of > 500ms (confirmed by repeat ECG)
    - Monitor ECGs frequently to confirm that the QTc interval as returned to baseline.
    - If syncope occurs, obtain an ECG to detect QT prolongation.
- **LFTs**: at baseline, and repeated monthly
  - If aspartate aminotransferase (AST) or alanine transaminase (ALT) exceeds 5 times the upper limit of normal then the regimen should be reviewed and bedaquiline and/or any hepatotoxic background medicinal product should be discontinued.
- **U&Es, calcium and magnesium**: at baseline and repeated if QT prolongation is detected.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Alcohol: can increase risk of hepatotoxicity. Manufacturer advises to avoid.
- Anti-arrhythmics: risk of prolonged QT interval (e.g. amiodarone, sotalol, procainamide, dysopyramide and quinidine).
- Antiretrovirals: limited data. Use https://www.hiv-druginteractions.org/checker to check for interactions.
- Antidepressants (tricylic): risk of prolonged QT interval.
- Antiemetics (domperidone, ondasetron): 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: co-administration of bedaquiline and medicinal products that induce CYP3A4 may decrease bedaquiline plasma concentrations and reduce its therapeutic effect. Co-administration of bedaquiline and moderate or strong CYP3A4 inducers should therefore be avoided for more than 14 days. If co-administration is required, more frequent electrocardiogram monitoring and monitoring of transaminases is recommended.
- Fluoroquinolones: risk of prolonged QTc interval.
- Macrolides: risk of prolonged QTc interval. Avoid co-administration for more than 14 days.
- Phenytoin: accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
- Rifampicin, rifabutin & rifapentine: accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
- St John's wort: accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Pregnancy:** Limited data on the use of bedaquiline in pregnant women. Use should be avoided unless the benefit is considered to outweigh the risks
  - **Breastfeeding:** There is very limited information regarding use of bedaquiline during breastfeeding. Based on data available, bedaquiline looks to pass into breastmilk in significant amounts. Use should be avoided unless the benefit is considered to outweigh the risks
  - **Hypersensitivity** to bedaquiline.
  - **QTc interval** > 500ms
  - **Ventricular arrhythmia**
  - **Lactose intolerance**

- **Cautions:**
  - **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 bedaquiline, ECGs should be monitored closely in patients:
    - Taking other QT prolonging drugs
    - With a history of Torsade de Pointes, congenital long QT syndrome, hypothyroidism and bradyarrhythmia, or uncompensated heart failure
    - With serum calcium, magnesium, or potassium levels below the lower limits of normal.
- **HIV co-infection**: limited information on the use of bedaquiline when co-administered with anti-retrovirals
- **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. Other hepatotoxic medicinal products should be avoided with bedaquiline, especially in patients with diminished hepatic reserve.
- **Renal disease**: use with caution in patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis.

NTM Network UK
Non-tuberculous mycobacteria

CEFOXITIN

*Please note **CEFOXITIN** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults:** 2g-4g two to three times a day (intravenous injection or infusion). Maximum 12g per day. Guidelines in cystic fibrosis recommend 200mg/kg/ day in 3 divided doses (maximum 12g per day)

Practice Point: the optimum dose has not been established. Dosing range reflects variation in practice determined by factors such as patient ideal body weight, potential interactions, co-morbidities and estimated mycobacterial load

- **Children:**
  - 12 years and above: dose as per adults
  - 3 months – 11 years: 150mg/kg/day in 2-4 divided doses (intravenous infusion) Maximum 12g per day.
- **Renal Impairment:** reduce dose in renal impairment and dialysis; consult a pharmacist for advice on dose reduction.
- **Hepatic Impairment:** no dose adjustment required
- **Obesity:** seek advice from a pharmacist

PATIENT COUNSELLING

- Common side effects may include rash, urticaria, abdominal pain, diarrhoea, nausea and vomiting.
- Advise patients to contact their doctor if diarrhoea becomes severe or persistent, or if there is blood or mucus in it, as this can be life-threatening. Also advise to not take medicines that stop or slow down bowel movements.
- Advise patients to contact their doctor if they have any unexplained fever, nosebleeds or bleeding gums, paleness or extreme fatigue, due to the risk of blood abnormalities (eosinophilia, leukopenia, neutropenia, agranulocytosis, anaemia, thrombocytopenia, medullary hypoplasia).
- Rarely, cefoxitin may have a risk of encephalopathy (which may result in confusion, loss of consciousness, seizure, abnormal movements). Report any symptoms to your doctor.
- Due to neurological side effects, cefoxitin may impair the performance of skilled tasks (e.g. driving and operating machinery)

PHARMACOKINETICS

- **Absorption:**
  - 100% bioavailability with intravenous administration.
- **Distribution:**
  - 50-80% protein bound.
  - Poorly penetrates the central nervous system (CNS).
- **Metabolism:**
  - Cefoxitin does not undergo any significant biotransformation.
- **Excretion:**
  - Up to 99% of cefoxitin is eliminated unchanged by the kidney.
- **Cmax:**
  - 220 mg/L (2g dose)
- **Tmax:**
  - 3 minutes after intravenous injection

- **Half-life:**
  - 45 minutes
  - Prolonged in renal impairment: >6 hours with creatinine clearance 10-30mL/min; >13 hours with creatinine clearance <10mL/min.

PREPARATIONS

- **Parenteral:** 1g and 2g vials (as powder for solution for injection or infusion)

DRUG LEVEL MONITORING

- Drug level monitoring for cefoxitin is unavailable in the UK

ADVERSE EFFECTS

- **Common**
  - **Cardiovascular:** hypotension
  - **Dermatological:** maculopapular rash, urticaria, injection site disorder, pruritus, fever
  - **Gastrointestinal:** abdominal pain, diarrhoea, nausea, vomiting
  - **Haematologic:** leucopenia, thrombocytopenia, , eosinophilia, neutropenia
  - **Hepatic:** transient increase in liver enzymes (ALT, AST, alkaline phosphatase (ALP))
  - **Local site reactions:** thrombophlebitis, phlebitis
  - **Renal:** raised serum creatinine (Jaffé test)
- **Serious**
  - **Dermatological:** erythema multiforme, Stevens-Johnson syndrome
  - **Gastrointestinal:** pseudomembranous colitis
  - **Haematologic:** anaemia, leucopenia, neutropenia, thrombocytopenia
  - **Hepatic:** cholestasis, jaundice
  - **Hypersensitivity reaction:** anaphylaxis
  - **Neurologic:** seizures
  - **Renal:** acute renal failure

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- **Anticoagulants:** potentiation of oral anticoagulant activity
- **Nephrotoxic medication:** increased risk of nephrotoxicity when administered with other nephrotoxic drugs e.g. amikacin
- **Probenecid:** increased plasma concentrations of cefoxitin

- **Interference with laboratory tests:**

- Coombs test: false-positive results may occur in patients treated with cefoxitin.
- Glycosuria: false-positive results may be observed with reduction substances, however, no interaction has been observed with enzymatic methods.
- Jaffe (picric acid) serum creatinine test may show falsely high creatinine values. Do not perform this assay on serum samples taken less than 2 hours after administration of cefoxitin.
- Urinary 17-hydroxy-corticosteroid: Porter Silber reaction may give moderate, falsely increased results in patients with high urinary concentrations of cefoxitin.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity:** to cefoxitin or other cephalosporins, and history of severe hypersensitivity to other types of beta-lactam antibacterial drugs
  - **Breastfeeding:** cefoxitin is excreted in human milk. Treatment with cefoxitin should be discontinued in lactating women to prevent any allergic reaction in the infant
- **Cautions:**
  - **Hypersensitivity:** patients with a history of non-severe hypersensitivity to other beta-lactam agents.
  - **Immunologic:** patients with hypersensitivity to penicillins or history of drug allergy
  - **Gastrointestinal:** history of gastrointestinal disease, particularly colitis
  - **Neuromuscular:** cefoxitin can potentially exacerbate myasthenia gravis
  - **Pregnancy:** limited data; use in pregnancy should be used only when clinically needed
  - **Renal:** dose adjustment required in renal impairment

NTM Network UK
Non-tuberculous mycobacteria

CIPROFLOXACIN

*Please note **CIPROFLOXACIN** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults**: 500mg – 750mg oral twice a day

Practice Point: the optimum dose has not been established. Dosing range reflects variation in practice determined by factors such as patient ideal body weight, potential interactions, co-morbidities and estimated mycobacterial load

- **Children**: limited data on evidence for dosing in NTM. These doses are based on ciprofloxacin oral dosing for respiratory tract infections as per the BNF for children, September 2022. Where possible, avoid in paediatrics due to concerns about arthropathy.
  - **Child:** 20 mg/kg twice daily (max. per dose 750 mg).
- Dose may need to be adjusted in severe renal impairment; seek advice from a pharmacist.

PATIENT COUNSELLING

- Can be taken with or without food. Swallow this medicine whole. Do not chew or crush
- Do not take milk, indigestion remedies or medicines containing iron or zinc, 2 hours before or after you take this medicine.
- Avoid direct exposure to either extensive sunlight or UV irradiation during treatment
- Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Therefore stop treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling. The MHRA has produced an advice sheet, which should be provided to patients and their carers.
- Due to the small increased risk of aortic aneurysm and dissection, seek immediate medical attention if sudden-onset severe abdominal, chest, or back pain develops.
- Seek immediate medical attention if experience a rapid onset of shortness of breath (especially when lying down flat in bed), swelling of the ankles, feet, or abdomen, or new-onset heart palpitations.
- Nerve damage (neuropathy) is a rare side effect. Report any abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in your body, especially in the legs or arms, or difficulty walking.
- Psychiatric reactions are a rare side effect. Report any symptoms of severe tiredness, depressed mood, anxiety, or problems with your memory or severe problems sleeping
- Due to neurological side effects, ciprofloxacin may impair performance of skilled tasks (e.g. driving and operating machinery)
- Patients with diabetes should monitor for hyperglycaemia or hypoglycaemia and report any concerns with their glycaemic control.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Rapid and extensive absorption. The absolute bioavailability is approximately 70-80%.
- **Distribution:**
  - 20-30% protein bound, present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight.
  - Achieves high concentrations in a variety of tissues such as lungs, kidneys, gallbladder, liver, gynaecological tissue and prostatic tissue, where total concentrations exceed those of

plasma concentrations.
  - Cerebrospinal fluid (CSF) concentrations range from 2.9% to 40% with noninflamed meninges to 24.1% to 91.1% with inflamed meninges.
- **Metabolism:**
  - Low concentrations of four metabolites have been reported which display in-vitro antimicrobial activity but to a lower degree than the parent compound.
- **Excretion:**
  - Largely excreted unchanged both renally and, to a smaller extent, faecally.
- **Cmax:**
  - Single doses of 100-750mg achieve dose-dependent Cmax of 0.56 - 3.7mg/L.
- **Tmax:**
  - 1 - 1.5 hours
- **Half-life:**
  - 4 - 7 hours (normal renal function)
  - Increased up to 12 hours in severely impaired renal function.

PREPARATIONS

- **Parenteral:** 200mg in 100mL, 400mg in 200mL Intravenous Infusion
- **Oral**: 100mg, 250mg, 500mg, 750mg tablets; 250mg/5mL granules and solvent for oral suspension

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Known or suspected malabsorption
  - Poor treatment response.
- **Target Level:**
  - Limited data. Target levels depend on MIC. For doses of 500mg twice daily, target levels have been suggested:
  - Trough (pre dose): 1mg/L
  - Peak (post dose): 3mg/L.
- **Timing of Sample:**
  - Trough: immediately before a dose
  - Peak: 2-hour post-oral dose sample
- **Frequency of Levels:**
  - No need for regular monitoring.
- **Suggested actions:**
  - The appropriate action in response to low levels is uncertain. A level under 1mg/L, with poor clinical progression, may suggest inadequate dosing
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information

ADVERSE EFFECTS

- **Common**
  - Metabolism: decreased appetite
  - Psychiatric: psychomotor hyperactivity / agitation
  - Gastrointestinal: nausea, diarrhoea, vomiting, gastro-intestinal and abdominal pains, dyspepsia, flatulence

  - Neurological: headache, dizziness, sleep disorders, taste disorders
  - Hepatobiliary: increase in transaminases, increased bilirubin
  - Dermatological: rash, pruritus, urticaria
  - Musculoskeletal, connective tissue and bone disorders: musculoskeletal pain, arthralgia
  - Renal: renal impairment
  - General: asthenia, fever

- **Serious**
  - Cardiovascular: QTc prolongation (rare)
  - Haematological: leukopenia, anaemia, neutropenia, leukocytosis, thrombocytopenia, thrombocythemia, haemolytic anaemia, agranulocytosis, pancytopenia (life- threatening), bone marrow depression (life- threatening), aortic aneurysm and dissection (rare)
  - Immunological: anaphylaxis, anaphylactic shock
  - Infection: pseudomembranous colitis
  - Metabolism and nutrition: hypoglycaemic coma, hyperglycaemia
  - Neurological: seizures, peripheral neuropathy
  - Gastrointestinal: pancreatitis, antibiotic-associated colitis
  - Hepatobiliary: hepatitis, liver necrosis (very rarely progressing to life- threatening hepatic failure)
  - Dermatological: Stevens-Johnson syndrome (potentially life- threatening), toxic epidermal necrolysis (potentially life- threatening)
  - Musculoskeletal, connective tissue and bone disorders: tendinitis, tendon inflammation and rupture, exacerbation of myasthenia gravis
  - Ophthalmic: visual disturbances (e.g. diplopia), visual colour distortions
  - Renal: renal failure, haematuria, crystalluria, tubulointerstitial nephritis

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- An ECG should be performed at baseline, 2 weeks and after the addition of any new medication that is known to prolong QT.
- **Calcium and magnesium**: at baseline and repeated if QT prolongation is detected.
- Blood glucose: should be monitored regularly in patients with diabetes (risk of hypoglycaemia)

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- **Aluminium**: reduced absorption of ciprofloxacin (take ciprofloxacin at least 2 hours before, or 2 hours after, aluminium-containing preparations)
- **Antacids**: reduced absorption of ciprofloxacin (take ciprofloxacin at least 2 hours before, or 2 hours after, antacids)
- **Anticoagulants**: enhanced anticoagulant effects of vitamin K antagonists (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione)
- **Antiemetics**: increased risk of QT prolongation (e.g. domperidone, metoclopramide, 5HT3 antagonists)
- **Calcium**: reduced absorption of ciprofloxacin (take ciprofloxacin at least 2 hours before, or 2 hours after, calcium-containing preparations)
- **Ciclosporin**: increased risk of nephropathy

- **Cinacalcet**: possible increased cinacalcet levels (monitor parathyroid hormone and serum calcium levels)
- **Clozapine**: increased clozapine serum levels (monitor for toxicity)
- **Dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice)**: reduced absorption of ciprofloxacin (avoid concurrent administration)
- **Drugs known to prolong the QT interval**: use with caution in patients taking class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics
- **Duloxetine**: increased serum levels of duloxetine expected
- **Iron**: reduced absorption of ciprofloxacin (take ciprofloxacin at least 2 hours before, or 2 hours after, iron-containing preparations)
- **Lidocaine**: reduced clearance of intravenous lidocaine (usually well tolerated, but monitor for increased side effects)
- **Magnesium**: reduced absorption of ciprofloxacin (take ciprofloxacin at least 2 hours before, or 2 hours after, magnesium-containing preparations)
- **Methotrexate**: increased methotrexate serum concentrations (increased risk of toxicity)
- **Mycophenolate**: modest reduction in mycophenolate concentrations may occur (unlikely to be clinically important, but in transplant patients monitor for graft rejection)
- **Phenytoin**: may result in increased or reduced serum levels of phenytoin (monitor serum phenytoin levels)
- **Phosphate binders (e.g. sevelamer, lanthanum carbonate)**: reduced absorption of ciprofloxacin (take ciprofloxacin at least 1–2 hours before, or 4 hours after, phosphate binders)
- **Pirfenidone**: increased pirfenidone levels (consider pirfenidone dose reduction)
- **Probenecid**: reduced renal excretion of ciprofloxacin (increased serum levels)
- **Ropinirole**: increased serum levels of ropinirole (monitor for increased side effects)
- **Sildenafil**: increased sildenafil serum levels (use with caution)
- **Theophylline**: increased serum levels of theophylline leading to increased risk of convulsions (reduce dose of theophylline and monitor levels)
- **Tizanidine**: increased tizanidine serum concentrations (potentiates hypotensive and sedative effect).

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - Concomitant administration of ciprofloxacin and tizanidine.
  - History of tendon disorders related to quinolone use
  - Allergy or serious adverse reactions in the past when using quinolone or fluoroquinolone containing products
  - Pregnancy and breastfeeding

- **Cautions:**
  - **Tendon Disorders**: ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder. Risk factors for tendon damage include age over 60 years and concomitant use of corticosteroids. If tendinitis is suspected, the quinolone should be discontinued immediately
  - **Aortic aneurysm and dissection**: risk-benefit should be assessed before prescribing ciprofloxacin in patients at risk of aortic aneurysm and dissection
  - **Myasthenia gravis:** use with caution, because symptoms can be exacerbated
  - **Visual Disorders**: if vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
  - **Neurological**: ciprofloxacin is known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with central nervous system (CNS)

disorders which may be predisposed to seizure.
- **Cardiovascular**: caution should be taken when using ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
  - congenital long QT syndrome
  - concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
  - uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
  - cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- **Glucose-6-phosphate dehydrogenase deficiency**: avoid unless the potential benefit is considered to outweigh the possible risk.

NTM Network UK
Non-tuberculous mycobacteria

CLARITHROMYCIN

*Please note **CLARITHROMYCIN** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults:** 500mg twice a day (oral). In non-severe MAC-pulmonary disease, a dose of 500mg twice a day, taken three times per week (oral) may be used.
- **Children over 12 years old and >30kg:** 500mg twice a day (oral)
- **Children under 12 years***:* Note: limited data on evidence for dosing in NTM. These doses are based on clarithromycin dosing for respiratory tract infections in the latest BNF for children December 2022 update
- **By mouth:** Child 1 month – 11 years (oral suspension advised):
    - body-weight under 8 kg: 7.5 mg/kg twice a day
    - 8–11 kg: 62.5mg twice a day
    - 12–19 kg: 125mg twice a day
    - 20–29 kg: 187.5mg twice a day
    - 30–40 kg: 250mg twice a day

- **Renal disease:** in patients with renal impairment who have creatinine clearance less than 30mL/min, the dosage of clarithromycin should be reduced to 50% of the normal recommended dose.
- **Hepatic disease:** no dose adjustment necessary. However, manufacturer advises caution; avoid in severe failure if renal impairment also present.
- **Obesity:** seek advice from a pharmacist.

PATIENT COUNSELLING

- Tablets and the suspension can be taken with or without food.
- Side effects may include abdominal pain, nausea, vomiting, altered taste, tinnitus, and hearing loss.
- Visual impairment and blurred vision may have an effect on a patient's ability to drive or operate machinery. The potential for dizziness, vertigo, confusion and disorientation, which may occur with clarithromycin, should be taken into account before patients drive or use machines.
- Patients with diabetes should monitor for hyperglycaemia or hypoglycaemia and report any concerns with their glycaemic control.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
    - Clarithromycin is rapidly and well absorbed from the gastrointestinal tract after oral administration. However first-pass metabolism reduces bioavailability to 55%
- **Distribution:**
    - Widely distributed into most body tissues with the exception of the central nervous system.
    - Clarithromycin is 80% bound to plasma proteins at therapeutic levels.
- **Metabolism:**
    - Undergoes extensive first pass metabolism in the liver resulting in the microbiologically active metabolite 14-hydroxyclarithromycin.

- **Excretion:**
  - 20% to 40% as unchanged drug is excreted in the urine with an additional 10% to 15% as metabolite.
  - Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5–10% of the parent drug is recovered from the faeces.
- **Cmax:**
  - 2.8 micrograms/mL (clarithromycin 500mg twice daily dosing).
- **Tmax:**
  - 2 hours
- **Half-life:**
  - 5- 6 hours. Prolonged in renal impairment

PREPARATIONS

- **Parenteral:** 500mg powder for solution for injection
- **Oral:** 250mg and 500mg tablets, 125mg/5mL and 250mg/5mL suspension, 250mg granule sachets

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

- **Common**
  - Gastrointestinal: abdominal pain, diarrhoea, nausea, vomiting and taste perversion.
  - Neurological: headache.
- **Serious**
  - Cardiovascular: QTc prolongation (very rare)
  - Dermatological: leucocytoclastic vasculitis, toxic epidermal necrolysis and Stevens-Johnson syndrome
  - Hepatic: hepatomegaly, hepatic dysfunction and hepatic failure (rare)
  - Immunological: anaphylaxis
  - Infective: *Clostridioides difficile*-associated diarrhoea and colitis
  - Ototoxicity: hearing loss and tinnitus reported in association with long-term use.

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- LFTs, U&Es and FBC should be checked at baseline.
- LFTs should be repeated at least every 6 months.
- ECG: baseline, 4 weeks and after the addition of any new medication that is known to prolong QT.
- **Calcium and magnesium**: at baseline and repeated if QT prolongation is detected.
- Ask about hearing loss, tinnitus and balance at every appointment. Consider baseline audiometry if there is a history of hearing difficulties and repeat if patients report any hearing loss or tinnitus.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests

(LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Use with caution with antivirals:
  - *Increased plasma concentrations of*: atazanavir, etravirine, nevirapine, telaprevir, tipranavir, and possibly maraviroc, rilpivirine.
  - *Increased clarithromycin concentrations with*: atazanavir, ritonavir, telaprevir, tipranavir.
  - *Reduced clarithromycin concentrations with:* etravirine, nevirapine.
  - *Increased risk of ventricular arrhythmias* with: saquinavir and telaprevir.
- *Increased plasma concentrations of*:
  - Antiepileptics: carbamazepine, phenytoin (monitor plasma concentrations).
  - CFTR modulators: increased plasma concentration of ivacaftor, tezacaftor, elexacaftor (co-administration is not recommended)
  - 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 with simvastatin and lovastatin, caution with others due to risk of rhabdomyolysis).
  - Tacrolimus (avoid clarithromycin, or monitor tacrolimus plasma concentrations).
  - Theophylline (reduce theophylline dose and monitor plasma concentrations).
  - Ticagrelor (avoid use).
  - Oral midazolam (avoid use)
- *Reduced clarithromycin concentrations with:*
  - CFTR modulators: Orkambi (lumacaftor/ivacaftor) may reduce clarithromycin plasma concentrations (co-administration is not recommended; consider azithromycin)
  - CYP3A4 inhibitors (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort): may reduce clarithromycin concentrations. The impact of rifampicin on clarithromycin is uncertain, but azithromycin may be preferred

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity**: to macrolides.
  - **Use of other drugs that may prolong the QT interval.**
  - **Renal & hepatic disease**: avoid in patients with a combination of both severe renal and hepatic disease.
  - **Past medical history of QT prolongation or ventricular cardiac arrhythmia**
- **Cautions:**
  - **Pregnancy & Breastfeeding.**
  - **Renal Disease:** use with caution and reduce dose if necessary.
  - **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.

NTM Network UK
Non-tuberculous mycobacteria

CLOFAZIMINE

*Please note **CLOFAZIMINE** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults**: 100–200mg once daily (oral).

Doses of 200mg daily for 2 months, then 100mg daily have been used. (Doses up to 300mg once daily have been used in leprosy.)

Practice Point: the optimum dose has not been established. Dosing range reflects variation in practice determined by factors such as patient ideal body weight, potential interactions, co-morbidities and estimated mycobacterial load

- **Children**: limited data, WHO recommendations for MDR-TB and XDR-TB are based on experience and expert opinion, and suggest 3–5 mg/kg/day (maximum 100 mg/day). Close monitoring is recommended due to limited experience.

- **Renal impairment**: caution in severe renal impairment
- **Hepatic impairment:** use with caution in patients with hepatic impairment [Child-Pugh classification A, B and C]. Check for viral hepatitis (hepatitis B and C). Do not use unless the benefits outweigh the risks.

PATIENT COUNSELLING

- Should be taken with a meal or with milk to maximise absorption because of the highly lipophilic nature of the drug.
- Clofazimine will cause skin discoloration and conjunctival pigmentation. This may take several months or years to disappear after the end of treatment. Report any visual disturbances. It will also cause discolouration of body secretion, including sweat, tears, sputum, urine and faeces.
- Vomiting: if the patient vomits within 1 hour of administration, the patient should take an extra dose. If vomiting occurs more than an hour after taking the dose, the patient does not need to take an extra dose and can take the next dose as usual when it is due.
- Clofazimine may cause dizziness or fatigue. If affected, do not drive or operate machinery.
- Advise patients to use sun blockers if on clofazimine and exposed to sun.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - 45% to 62% absorption rate after oral administration
  - Taking clofazimine with food increases the bioavailability and accelerates absorption rate.
- **Distribution:**
  - Clofazimine is highly lipophilic and tends to be deposited predominantly in fatty tissue and in cells of the reticuloendothelial system.
  - Does not cross blood-brain barrier.
- **Metabolism:**
  - Undergoes hepatic metabolism to three metabolites
- **Excretion:**
  - Unchanged clofazimine is excreted via the bile mainly in the faeces.

  - A small amount is also eliminated in the sputum, sebum, and sweat.
- **Cmax:**
  - 0.145mg/L after a 200mg fasting dose.
- **Tmax:**
  - 6-8 hours when taken with food, increasing to 12 hours when taken without food.
- **Half-life:**
  - 25 days (range 6.5 to 160 days) following repeated oral doses of 50 or 100mg

PREPARATIONS

- **Oral:** 50mg and 100mg capsules
  Clofazimine is available through specialist pharmaceutical wholesale importers

DRUG LEVEL MONITORING

- Drug levels cannot currently be performed in the UK

ADVERSE EFFECTS

- **Common**
  - Dermatological: pigmentation from pink to brownish-black in 75% to 100% of the patients within a few weeks of treatment; ichthyosis and dryness; rash and pruritus.
  - Gastrointestinal: abdominal and epigastric pain, diarrhoea, nausea, vomiting, gastrointestinal intolerance.
  - Ocular: diminished vision, conjunctival and corneal pigmentation due to clofazimine crystal deposits, dryness, burning, itching, irritation.
  - Other: discoloration of urine, faeces, sputum, sweat; elevated blood sugar; elevated erythrocyte sedimentation rate (ESR).
- **Serious**
  - Cardiovascular QT interval dysfunction which correlates with serum concentration
  - Liver dysfunction
  - Gastrointestinal: (<1%): bowel obstruction, gastrointestinal haemorrhage
  - Ophthalmic: conjunctival pigmentation, subjective dimness of vision, and dry eyes, burning and other ocular irritation
  - Psychiatric: reactive depression due to skin discolouration
  - Other: splenic infarction, discolouration of body fluids.

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- ECG: baseline, 4 weeks and after the addition of any new medication that is known to prolong QT.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- **Rifampicin:** 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
- **Drugs that prolong QT interval**: increased risk of prolonged QTc with other drugs that prolong QTc including fluoroquinolones, bedaquiline, delamanid, efavirenz and several other antiretrovirals for the treatment of HIV, or azole anti-fungals.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - Hypersensitivity to clofazimine or to any of the excipients contained in the formulation.
  - Hypersensitivity: to peanuts or soya, as clofazimine capsules contain soybean oil.
- **Cautions:**
  - Cardiac disease: patients at risk of prolongation of QT interval
    - With congenital or documented QT prolongation.
    - Currently receiving treatment with other active substances known to prolong QT interval
    - With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
    - With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.
  - **Pregnancy**
  - **Breastfeeding:** note that limited published evidence has shown potentially significant quantities of clofazimine are excreted into breast milk with reddish/pink discolouration of milk and infants' skin may occur.
  - **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

NTM Network UK
Non-tuberculous mycobacteria

CO-TRIMOXAZOLE (TRIMETHOPRIM/SULFAMETHOXAZOLE)

*Please note **CO-TRIMOXAZOLE** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults**:
  - 960mg TWICE a day (oral or intravenous)
  - 1.44g TWICE day (intravenous) - cystic fibrosis (CF) patients
- **Children**:
  - 10-20mg/kg/dose TWICE a day (oral or intravenous)

- **Renal impairment**: reduce dose in renal impairment; discuss with a pharmacist
- **Hepatic impairment**: no information available relating to dose in impaired hepatic function. Avoid in severe hepatic impairment

PATIENT COUNSELLING

- Take tablets or oral suspension with food or drink to minimise gastro-intestinal disturbance, but can be taken on an empty stomach
- Advise patient to report any rash, skin reactions, sore throats and fevers
- Advise patients to report any ulcers in the mouth, throat, nose, genitals and conjunctivitis
- Advise patients to report any unexpected worsening of cough and shortness of breath.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Rapid and near complete absorption (bioavailability near 100%)
- **Distribution:**
  - Rapidly distributed in the body due to lipophilic properties. Tissue levels of trimethoprim exceed plasma concentrations, particularly lungs and kidneys
  - Protein binding - 50% trimethoprim, 66% sulfamethoxazole
  - Cerebrospinal fluid (CSF) levels of trimethoprim and adequate for antibacterial activity
- **Metabolism:**
  - Sulfamethoxazole is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation.
  - Caution should be exercised when treating patients with severe hepatic parenchymal damage as there may be changes in the absorption and biotransformation of trimethoprim and sulfamethoxazole.
- **Excretion:**
  - The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug.
  - Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely.
  - The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form.
- **Cmax:**
  - Trimethoprim 5-10mg/L

- Sulfamethoxazole 120-150mg/L
- **Tmax:**
  - 1-4 hours
- **Half-life:**
  - Trimethoprim: 8.6 to 17 hours. Increased by a factor of 1.5 to 3.0 in severe renal impairment (Creatinine Clearance <10mL/min)
  - Sulfamethoxazole: 9 to 11 hours (normal renal function).
  - Elimination half-life is reduced in patients with Cystic Fibrosis.

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PREPARATIONS

- **Parenteral:** 480mg/5mL (sulfamethoxazole/trimethoprim 400mg/80mg per 5mL) solution for infusion
- **Oral:** 480mg (sulfamethoxazole/trimethoprim 400mg/80mg) and 960mg (sulfamethoxazole/trimethoprim 800mg/160mg) tablets, 240mg/5mL (sulfamethoxazole/trimethoprim 200mg/40mg per 5mL) and 480mg/5mL (sulfamethoxazole/trimethoprim 400mg/80mg per 5mL) oral suspension

Note the formulation ratio is 1:5 of trimethoprim to sulfamethoxazole

DRUG LEVEL MONITORING

Caution: Therapeutic drug monitoring (TDM) in NTM is not validated

- **Indications for monitoring:**
  - Significant renal impairment
  - Suspected malabsorption
- **Target Level:**
  - Sulfamethoxazole:
    - Trough (pre dose): <100mg/L
    - Peak (post dose): 120-150mg/L but <200mg/L
  - Trimethoprim:
    - Trough (pre dose): 5-7mg/L
    - Peak (post dose): 5-10 but <20mg/L
  - NB. Post dose levels are usually reserved for high dose treatment in Pneumocystis pneumonia - discuss with pharmacist if considering post dose sample for NTM treatment
- **Timing of Sample:**
  - Trough: immediately before a dose
  - Peak: 1 hour after the end of intravenous administration or 2 hours after oral administration
- **Frequency of Levels:**
  - Repeated levels not usually required but consider 6-8 days after dose change
- **Suggested actions:**
  - Low levels: consider dose increase in the context of poor response
  - High levels: consider dose reduction.
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information

ADVERSE EFFECTS

- **Common**
  - Dermatological: rash
  - Gastrointestinal: nausea, diarrhoea
  - Infections: fungal overgrowth/candida

  - Metabolic: hyperkalaemia
  - Neurological: headache
- **Serious**
  - Dermatological: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) - all rare, photosensitivity
  - Gastrointestinal: pseudomembranous colitis, pancreatitis (very rare)
  - Haematological (very rare): leukopenia, neutropenia, thrombocytopaenia, agranulocytosis, haemolysis in certain G-6-PD deficient patients, megaloblastic anaemia, aplastic anaemia, eosinophilia, purpura, methaemoglobinaemia
  - Hepatic: cholestatic jaundice, hepatic necrosis (very rare)
  - Immunological (very rare): serum sickness, anaphylaxis, allergic myocarditis, systemic lupus erythematosus (SLE), hypersensitivity vasculitis
  - Metabolic: hypoglycaemia, hyponatraemia (very rare)
  - Neurological: aseptic meningitis, convulsions, peripheral neuropathy (very rare)
  - Psychiatric: depression/hallucination (very rare)
  - Renal: crystalluria, interstitial nephritis, acute tubular necrosis
  - Respiratory: cough/fever/dyspnoea with pulmonary infiltrates/acute respiratory distress syndrome (ARDS) (very rare)

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- **FBC**: consider monthly in all patients due to risk of asymptomatic folate deficiency
- **Elderly patients**: consider monthly monitoring as increases risk of adverse effects e.g. U&Es/LFTs/FBC
- **Patients at risk of hyperkalaemia**: close monitoring of serum potassium

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers/potassium sparing diuretics: increased risk of hyperkalaemia
- Ciclosporin/tacrolimus: increased risk of renal impairment
- Clozapine: increased risk of bone marrow suppression
- Digoxin: increase in digoxin levels in some elderly patients
- Folinic acid: interferes with antimicrobial activity
- Methotrexate: potential increase in free plasma levels of methotrexate
- Phenytoin: prolonged half-life of phenytoin
- Repaglinide: increased exposure of repaglinide
- Sulfonylureas: potentiation of effect, especially with higher doses
- Thiazides: increased risk of thrombocytopaenia
- Warfarin: potentiates anticoagulant effect

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to sulphonamides or trimethoprim
  - **Acute porphyria**
  - **Pregnancy**
  - **Haematological**: serious haematological disorders (except under careful supervision)
  - **Hepatic:** severe hepatic impairment
  - **Immunological**: history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.
- **Cautions:**
  - **Renal**: severe renal insufficiency (unless TDM available)
  - **Glucose -6-phosphate dehydrogenase deficiency**: risk of haemolysis
  - **Porphyria**: avoid in people with or at risk of porphyria due to exacerbation of porphyria
  - **Breastfeeding** where there is a risk of the infant developing hyperbilirubinaemia
  - **Severe atopy/asthma**

NTM Network UK
Non-tuberculous mycobacteria

ETHAMBUTOL

Please note ETHAMBUTOL is not licensed for the treatment of NTM in the UK.

DOSAGE (Note that ethambutol should be dosed using ideal body weight)

- **Adults**: 15mg/kg once daily (oral). Max dose 1.6g. In non-severe MAC-pulmonary disease, a dose of 25mg/kg three times weekly may be used.
- **Obesity** (consider for patients with BMI >30): it has been suggested that obese patients should have their dose adjusted based on an ideal body weight plus 40% of the excess weight (Adjusted body weight [AjBW]). The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.
  Male IBW (kg) = 50 + (0.91 x [height in cm - 152.4])
  Female IBW (kg) = 45.5 + (0.91 x [height in cm - 152.4])
  Adjusted body weight (AjBW) = IBW + (0.4 x [ABW-IBW])

- **Children**: 20mg/kg once daily (oral)

- Round doses to nearest tablet strength.

  - **Renal impairment:** dose reduction required; discuss with a pharmacist. Avoid in severe renal impairment where possible due to risk of optic nerve damage.

PATIENT COUNSELLING

- Tablets can be taken with or without food
- Report any visual disturbances

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - 80% of an oral dose is absorbed from gastrointestinal tract.
- **Distribution:**
  - Distributes widely throughout body, and concentrates in lungs, kidneys, saliva, and red blood cells.
  - Does not cross blood-brain barrier with non-inflamed meninges. Cerebrospinal fluid (CSF) levels are 10- 50% of plasma when meninges are inflamed.
- **Metabolism:**
  - 20% of the drug is metabolised by the liver to an inactive metabolite.
- **Excretion:**
  - 50% is excreted unchanged in the urine with up to about 20% excreted in faeces within 48 hours.
- **Cmax:**
  - Up to 5mg/L
- **Tmax:**
  - 2-4 hours
- **Half-life:**
  - 3-4 hours

PREPARATIONS

- **Oral**: 400mg and 100mg tablets; 400mg/5mL oral suspension (specially manufactured 'special' unlicensed product)
- **Parenteral**: 1g/10mL infusion (unlicensed product may be available from specialist importers)

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Drug levels are not required routinely but recommended in:
  - Known or suspected malabsorption
  - Renal impairment
  - Poor treatment response
- **Target Level:**
  - Trough (pre dose): <1mg/L
  - Peak (post dose): 2-6mg/L
- **Timing of Sample:**
  - Trough: immediately before a dose is taken
  - Peak: 2 hours after a dose is taken. Consider repeating at 6 hours if suspected delayed or malabsorption.
- **Frequency of Levels:**
  - Levels do not need to be repeated routinely. Consider repeating in changing renal function
- **Suggested actions:**
  - High peak level: monitor for visual disturbance and consider dose reduction
  - Low peak level: repeat levels at 2- and 6-hrs post dose to determine any delayed or malabsorption; depending on outcome consider dose increase.
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information
  - Cardiff and Vale University Health Board Medical Biochemistry and Immunology Department: https://cavuhb.nhs.wales/our-services/laboratory-medicine/medical-biochemistry-and-immunology/

ADVERSE EFFECTS

- **Common**
  - **Endocrine**: hyperuricaemia;
  - **Gastrointestinal**: nausea and vomiting
- **Serious**

Ophthalmic: optic neuritis risk is greatest at doses >25mg/kg/day, or when treatment duration >2months; including diabetic patients and those at higher risk of ethambutol accumulation such as renal impairement. Note that the first sign of an ocular toxic reaction to ethambutol can be red/green colour vision disturbance before a reduction in visual acuity, hence if patients are already red/green colour blind pre-treatment, opthalmic adverse effect monitoring might be challenging.

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- **Ophthalmic**: visual acuity via Snellen chart test and colour discrimination via Ishihara plates

testing to be done at baseline, repeated at two months and at least every 6 months. Patients should be asked about symptoms at every appointment.
- Patients at higher risk of ophthalmic toxicity (children, doses >15mg/kg/day, renal impairment), we recommend monthly visual acuity and colour differentiation tests with symptom screen
- Any reported visual disturbance should result in prompt referral for formal ophthalmology assessment.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Aluminium hydroxide may impair the absorption of ethambutol, therefore antacids containing this ingredient should be avoided during treatment with ethambutol.
- 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

- **Contra-indications**:
  - **Hypersensitivity** to ethambutol
  - **Optic neuritis**: patients with known optic neuritis and poor vision unless clinical judgement determines it may be for use.
- **Cautions:**
  - **Renal impairment**: reduce dose
  - **Young children**: due to difficulty in testing eyesight and obtaining reports on symptomatic visual changes
  - **Elderly patients**: due to the risk in ophthalmic adverse effects
  - **Pregnancy and breastfeeding**: manufacturer advises that it may be considered for use if benefits to the mother outweigh potential risks to the child.

NTM Network UK
Non-tuberculous mycobacteria

IMIPENEM-CILASTATIN

Please note IMIPENEM-CILASTATIN is not licensed for the treatment of NTM in the UK.

DOSAGE

- **Adults**: imipenem 1000mg two to three times daily (intravenous). Consider 500mg two to three times daily (intravenous) for small, frail or elderly patients.
- **Children**: imipenem 15–20mg/kg twice daily (maximum dose 1000mg). Use with caution; meropenem is the preferred carbapenem in children <15 years.

Practice Point: the optimum dose has not been established. Dosing range reflects variation in practice determined by factors such as patient ideal body weight, potential interactions, co-morbidities and estimated mycobacterial load

- **Renal impairment**: use with caution (meropenem preferred). Dose may need to be adjusted in renal impairment, please discuss with a pharmacist.

PATIENT COUNSELLING

- Common side effects include nausea, vomiting, diarrhoea, injection site reactions (e.g. redness and swelling along the vein) or rash.
- Severe nausea and vomiting are common. Consider prescribing and optimising regular anti-emetics to support the patient to tolerate treatment.
- Imipenem-cilastatin is given intravenously (into a vein) over 40-60 minutes. The rate of infusion may be slowed if patients feel nauseated.

PHARMACOKINETICS

- **Absorption:**
  - 100% bioavailability with intravenous administration.
- **Distribution:**
  - The ratio of lung epithelial lining fluid to plasma ratio is 44%.
  - Imipenem is ~20% protein bound, cilastatin is ~40% protein bound.
- **Metabolism:**
  - Imipenem is metabolized in the kidney by dehydropeptidase I.
  - Cilastatin is a specific inhibitor of dehydropeptidase I enzyme and effectively inhibits metabolism of imipenem.
- **Excretion:**
  - Imipenem and cilastatin are primarily renally excreted.
  - When given with cilastatin, about 70% of imipenem is recovered unchanged in the urine within 10 hours, and the remainder is excreted in the urine as inactive metabolites
- **Cmax:**
  - Imipenem: 39 mg/L with 500/500 mg dosing; 66 mg/L with 1000/1000 mg dosing.
  - Cilastatin: 42 mg/L with 500/500 mg dosing; 72 mg/L with 1000/1000 mg dosing.
- **Tmax:**
  - 20 minutes post-infusion
- **Half-life:**
  - Imipenem: 1 hour
  - Cilastatin: 1 hour

PREPARATIONS

- **Parenteral**: 500mg/500mg powder for solution for infusion

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured
- Drug level monitoring is not known to be available in the UK.

ADVERSE EFFECTS

- **Common**
  - Dermatologic: rash
  - Gastrointestinal: diarrhoea, vomiting, nausea
  - Haematologic: eosinophilia
  - Hepatic: increases in serum transaminases, increases in serum alkaline phosphatase
  - Vascular: thrombophlebitis
- **Serious**
  - Dermatologic: toxic epidermal necrolysis, angioedema, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis
  - Haematologic: pancytopenia, neutropenia, leukopenia, thrombocytopenia, thrombocytosis, agranulocytosis (rare)
  - Hepatic: increase in transaminases, hepatic failure and fulminant hepatitis
  - Immunologic: serious and occasionally fatal hypersensitivity (anaphylactic) reactions
  - Infections: antibiotic-associated colitis and pseudomembranous colitis
  - Neurologic: myoclonic activity, confusional states, or seizures, especially with excessive doses are used based on renal function and body weight.
  - Renal: acute renal failure, oliguria/anuria, polyuria

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

Tests as per generic NTM drug monitoring guidelines.

INTERACTIONS

- Ganciclovir: increased risk of convulsions
- Valproic acid: reduced serum concentrations of valproate; avoid concomitant use
- Warfarin: potential for increased anticoagulant effect. Monitor INR frequently

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to active substances or excipients
  - **Hypersensitivity** to carbapenems, or other beta-lactam antibiotics
- **Cautions:**

- **Hepatic**: monitor LFTs closely during treatment in people with pre-existing liver disease
- **Valproic acid**: concomitant use of imipenem-cilastatin and valproic acid is not recommended
- **Clostridioides difficile**: consider antibiotic-associated colitis and pseudomembranous colitis in people who develop diarrhoea during treatment.
- **Neurologic**: do not use imipenem-cilastatin in people with central nervous system (CNS) disease
- **Renal**: increased risk of seizures in renal impairment due to accumulation of imipenem.
- **Children**: meropenem is preferred carbapenem in children <15 years
- **Pregnancy and breastfeeding**: limited data.

NTM Network UK
Non-tuberculous mycobacteria

ISONIAZID

Please note that ISONIAZID is not licensed for the treatment on NTM in the UK.

DOSAGE

- **Adults**: 300mg once a day (oral or intravenous). Consider 5mg/kg once a day if low body weight.
- **Children**: 10mg/kg (max 300mg) once a day (oral or intravenous).
- **Renal impairment**: dose may need to be adjusted in renal impairment; discuss with a pharmacist
- Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet.
- 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.

PATIENT COUNSELLING

- Isoniazid should be taken 30-60 minutes before food, or 2 hours after food.
- Common side effects include nausea, rash or itching, and peripheral neuropathy. Transient transaminitis is common and rarely, can cause liver damage, which should be monitored regularly.
- Report any tingling or numbness in the hands or feet (pins and needles), as this may be a symptom of peripheral neuropathy.
- Report any yellowing of the skin or whites of the eyes, darker urine and paler stools, nausea and vomiting.
- Isoniazid can sometimes cause dizziness or confusion. If affected, do not drive or operate machinery.
- Possible food interactions: there is a theoretical 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

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Isoniazid is readily and completely absorbed after oral administration (≥80%).
  - The rate and extent of absorption of oral isoniazid is reduced by food.
- **Distribution:**
  - Diffuses into all tissues and fluids including the cerebrospinal fluid. Isoniazid is 0-10% protein bound.
- **Metabolism:**
  - Isoniazid undergoes acetylation, hydrolysis and glycine conjugation, hydrazone formation, and n-methylation.
  - Acetylation is polymorphic and two groups of acetylators have been identified, rapid and slow acetylators. The rate of hydrolysis is more rapid in the rapid acetylators than in the slow ones.
- **Excretion:**
  - Over 90% of a dose is excreted in the urine in 24 hours, most being excreted in the first 12 hours. 4-32% is unchanged, but no more than 10% of a dose is excreted in the faeces.

- **Cmax:**
  - 5.4 ± 20mg/L in fast acetylators
  - 7.1 ± 1.9mg/L in slow acetylators
- **Tmax:**
  - 1 - 2 hours
- **Half-life:**
  - 1.2 and 3.5 hours in fast and slow acetylators respectively.

PREPARATIONS

- **Oral**: 100mg, 50mg tablets, unlicensed 'special' liquid
- **Parenteral**: 50mg/2mL injection
- **Note**: isoniazid is also available as a combination oral preparation with rifampicin:
  - Rifinah® 300/150mg tablets (rifampicin 300mg + isoniazid 150mg)
  - Rifinah® 150/100mg tablets (rifampicin 150mg + isoniazid 100mg)

DRUG LEVEL MONITORING

Some laboratories can measure isoniazid metabolite (N-acetyl isoniazid) levels to give an indication of acetylator status

- **Indications for monitoring:**
  - Can be measured if known or suspected malabsorption;
  - Poor treatment response.
- **Target Level:**
  - Peak (post dose): 3-5mg/mL
- **Timing of Sample:**
  - Peak: Level taken 2 hours post-dose. Repeat at 6 hours if suspect delayed absorption.
- **Frequency of Levels:**
  - Drug levels need not be routinely measured.
- **Suggested actions:**
  - Isoniazid post dose level: high - reduce the dose; low - increase dose
  - N-Acetyl isoniazid post dose level: Not validated. The timing and extent of Cmax may indicate whether patients are fast or slow acetylators.
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information
  - Cardiff and Vale University Health Board Medical Biochemistry and Immunology Department: https://cavuhb.nhs.wales/our-services/laboratory-medicine/medical-biochemistry-and-immunology/

ADVERSE EFFECTS

- **Common**
  - **Neurological**: peripheral neuropathy.
  - **Hepatic**: increases in transaminases and/or bilirubin especially when used in combination with rifampicin .
- **Serious**
  - **Dermatological**: skin reactions, for example urticaria (uncommon).
  - **Haematological**: agranulocytosis, megaloblastic anaemia, thrombocytopenia.
  - **Hepatic**: hepatotoxicity (rare).
  - **Immunological**: drug-induced lupus (rare).
  - **Musculoskeletal**: arthralgia, rhabdomyolysis.

- **Neurological**: seizure, psychosis (rare)

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

Tests as per generic NTM drug monitoring guidelines.

INTERACTIONS

- **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 monoamine oxidase by isoniazid.
- **Theophylline**: isoniazid may reduce clearance, monitor theophylline levels and adjust dose as necessary.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to isoniazid
  - **Hepatic:** drug-induced liver disease.
- **Cautions:**
  - **Endocrinology**: diabetes mellitus, chronic alcoholism,
  - **Renal:** impaired renal function,
  - **Hepatic**: liver disease concomitant use of other potentially hepatotoxic drugs; Risk factors for isoniazid induced hepatotoxicity include advanced age, female gender, slow acetylators, malnutrition, HIV infection, pre-existing liver disease and extra pulmonary tuberculosis - monitor LFTs closely.
  - **History of psychosis**.
  - **Neurologic**: patients with convulsive disorders, increased risk of peripheral neuropathy in people with or at risk of malnutrition, HIV infection, diabetes mellitus, uraemia, pregnancy and alcohol dependence
  - **Pregnancy:** Manufacturer advises that it may be considered for use if benefits to the mother outweigh potential risks to the child.
  - **Breastfeeding**: isoniazid passes into the breast milk in small quantities. Monitor breastfed infants for signs of toxicity. Consider administering pyridoxine to mother and breastfed infant.

NTM Network UK
Non-tuberculous mycobacteria

LEVOFLOXACIN

*Please note **LEVOFLOXACIN** is not licensed for the treatment of NTM in the UK.*

DOSAGE

Limited data on dosing, based on case reports only

- **Adults:** 750mg- 1000mg per day in one to two divided doses.
    - Reduce dose in renal impairment; discuss with a pharmacist

Practice Point: the optimum dose has not been established. Dosing range reflects variation in practice determined by factors such as patient ideal body weight, potential interactions, co-morbidities and estimated mycobacterial load

- **Children**: 15-20mg/kg once a day. Where possible, avoid in paediatrics due to concerns about arthropathy
    - Note: limited data on evidence for dosing in NTM. These doses are based on MDR-TB dosing based on WHO 2022 and Sentinel 2022 updates

PATIENT COUNSELLING

- Can be taken with or without food. Swallow this medicine whole. Do not chew or crush
- Do not take milk, indigestion remedies or medicines containing iron or zinc, 2 hours before or after you take this medicine.
- Avoid direct exposure to either extensive sunlight or UV irradiation during treatment
- Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Therefore stop treatment at the first signs of a serious adverse reaction, such as tendonitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling. The MHRA has produced an advice sheet, which should be provided to patients and their carers.
- Due to the small increased risk of aortic aneurysm and dissection, seek immediate medical attention if sudden-onset severe abdominal, chest, or back pain develops.
- Seek immediate medical attention if experience a rapid onset of shortness of breath (especially when lying down flat in bed), swelling of the ankles, feet, or abdomen, or new-onset heart palpitations.
- Nerve damage (neuropathy) is a rare side effect. Report any abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in your body, especially in the legs or arms, or difficulty walking.
- Psychiatric reactions are a rare side effect. Report any symptoms of severe tiredness, depressed mood, anxiety, or problems with your memory or severe problems sleeping
- Due to neurological side effects, levofloxacin may impair performance of skilled tasks (e.g. driving and operating machinery)
- Patients with diabetes should monitor for hyperglycaemia or hypoglycaemia and report any concerns with their glycaemic control.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
    - Levofloxacin is rapidly and almost completely absorbed. Bioavailability is approximately 99-100%.
- **Distribution:**

- Approximately 30–40 % of levofloxacin is bound to serum protein.
- The mean volume of distribution of levofloxacin is approximately 100L after single and repeated 500mg doses, indicating widespread distribution into body tissues.
- Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine.
- Levofloxacin has poor penetration into cerebrospinal fluid.

- **Metabolism:**
  - Levofloxacin is metabolised to a very small extent
- **Excretion:**
  - Levofloxacin is primarily excreted by the renal route (>85 % of the administered dose).
- **Cmax:**
  - 7-12mg/L
- **Tmax:**
  - 1-2 hours
- **Half-life:**
  - 6-8 hours

PREPARATIONS

- **Parenteral**: 500mg/100mL infusion bag
- **Oral**: 250mg and 500mg tablets

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Known or suspected malabsorption
  - Poor treatment response.
- **Target Level:**
  - Limited data. Target levels depend on minimum inhibitory concentration (MIC). For doses of 500mg twice daily, target levels have been suggested:
  - Trough (pre dose): 0.5 - 2mg/L
  - Peak (post dose): 8 - 13mg/L.
- **Timing of Sample:**
  - Trough: immediately before a dose is taken
  - Peak: 2-hour post-oral dose sample
- **Frequency of Levels:**
  - No need for regular monitoring.
- **Suggested actions:**
  - The appropriate action in response to low levels is uncertain. A peak level under 8mg/L, with poor clinical progression, may suggest inadequate dosing
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information

ADVERSE EFFECTS

- **Common**
  - Gastrointestinal: diarrhoea, nausea, and vomiting
  - Skin: photosensitivity, rash
  - Hepatic: transient increases in LFTs
- **Serious**
  - Gastrointestinal: Clostridium difficile,

- Vascular: aortic aneurysm
- Cardiovascular: QTc prolongation (rare; more common in hypokalaemia, and predisposing cardiac conditions).
- Dermatological: Stevens-Johnson syndrome or toxic epidermal necrolysis (rare).
- Metabolic: hypoglycaemia (in patients on hypoglycaemic drugs, uncommon).
- Haematologic: eosinophilia, leukopenia (uncommon), thrombocytopaenia, neutropaenia (rare).
- Hepatic: acute hepatitis (rare).
- Immunological: anaphylaxis, immune hypersensitivity (uncommon).
- Musculoskeletal: tendon inflammation and rupture (see contra-indications below).
- Neurological: seizures (caution in patients with central nervous system (CNS) disorders).
- Renal: renal impairment (rare).

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- LFTs should be repeated at least every 6 months.
- ECG: baseline, 4 weeks and after the addition of any new medication that is known to prolong QT.
- **Calcium and magnesium**: at baseline and repeated if QT prolongation is detected.

Tests as per generic NTM drug monitoring guidelines.

INTERACTIONS

- Iron salts, zinc, magnesium or aluminium containing antacids decrease exposure to levofloxacin; levofloxacin should be taken 2 hours before or after antacids
- Non-steroidal anti-inflammatories: theoretical increased risk of seizures
- Coumarin anticoagulants: levofloxacin increased anticoagulant effect monitor INR
- Drugs known to prolong the QT interval: use with caution in patients taking Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics.
- Theophylline: increased risk of convulsions. Reduce dose of theophylline and monitor levels.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **History of tendon disorders** related to quinolone use
  - **Hypersensitivity** to quinolones or any excipient
  - **Pregnancy**: avoid in pregnancy; animal studies have shown quinolones cause arthropathy.
  - **Breastfeeding**: avoid, present in milk in animal studies.
  - **Children**: levofloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in NTM with caution; arthropathy has developed in weight-bearing joints of young animals.
- **Cautions:**
  - **Tendon damage** (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping a quinolone. Healthcare professionals are reminded that:

    - Quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use
    - Patients over 60 years of age are more prone to tendon damage
    - The risk of tendon damage is increased by the concomitant use of corticosteroids
    - If tendonitis is suspected, the quinolone should be discontinued immediately
- **Prolonged QTc interval** or risk factors for QTc prolongation
- **History of seizures**
- **Myasthenia Gravis**: risk of exacerbation
- **Diabetes**: may affect blood sugars
- **Aortic aneurysm and dissection, and heart valve regurgitation/incompetence**
- **Clostridium difficile**-associated disease
- **G-6-phosphate dehydrogenase deficiency**
- **Risk of heart valve regurgitation**
    - Congenital or pre-existing heart valve disease
    - Connective tissue disorders (e.g. Marfan syndrome or Ehlers-Danlos syndrome)
    - Other risk factors or conditions predisposing to heart valve regurgitation (e.g. hypertension, Turner's syndrome, Behçet's disease, rheumatoid arthritis, and infective endocarditis)

NTM Network UK
Non-tuberculous mycobacteria

LINEZOLID

*Please note **LINEZOLID** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults**: 600mg once a day (oral or intravenous).
- **Children 1-15kg**: 15mg/kg once a day
- **Children >16kg :** 10-12mg/kg once daily (maximum 600mg in 24 hours)

Note: limited data on evidence for dosing in NTM. These doses are based on MDR-TB linezolid dosing based on WHO 2022 and Sentinel 2022 updates.

- **Renal impairment**: no dosage adjustment required; use with caution in severe renal impairment due to accumulation of metabolites (unknown clinical significance)
- **Hepatic impairment**: no dosage adjustment required; use with caution due to limited data

PATIENT COUNSELLING

- Patients should be asked:
  - At each review (and encouraged to self-report) about any signs of a peripheral neuropathy/ paraesthesia (pin and needles) or reduced sensation of hands or feet.
  - To report symptoms of visual impairment
  - To report any unexplained bruising
- If any dizziness or symptoms of visual impairment, do not drive or operate machinery.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Linezolid is rapidly and extensively absorbed following oral dosing. The bioavailability of oral linezolid is approximately 100%.
  - Absorption is not significantly affected by food.
  - Absorption from the oral suspension is similar to film-coated tablets.
- **Distribution:**
  - The volume of distribution at steady-state averages at about 40-50 litres in healthy adults and approximates to total body water.
  - Plasma protein binding is about 31% and is not concentration dependent.
  - The ratio of lung epithelial lining fluid to serum levels is ≥100%, and the ratio of tissue to serum levels is approximately 49%.
  - The level of linezolid in the cerebrospinal fluid (CSF) is approximately 40% of blood levels.
- **Metabolism:**
  - Undergoes hepatic metabolism to two inactive metabolites.
- **Excretion:**
  - Linezolid is primarily excreted in the urine as the parent drug (30%) and two metabolites (50%).
- **Cmax:**
  - 12.7mg/L and 12.9mg/L after single intravenous and oral 600mg doses respectively.
- **Tmax:**
  - 2 hours
- **Half-life:**
  - 5-7 hours

PREPARATIONS

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

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Known or suspected malabsorption
  - Poor treatment response
  - Low body weight
  - Interacting medication
- **Target Level:**
  - Trough (pre dose): <5mg/L
  - Peak (post dose): 12-26mg/L
- **Timing of Sample:**
  - Trough: immediately before a dose is taken
  - Peak: 2 hours post oral dose OR 1 hour post intravenous infusion
- **Frequency of Levels:**
  - Regular monitoring is not recommended unless on-going concerns
- **Suggested actions:**
  - The appropriate action in response to low levels is uncertain. A peak level under 12mg/L, with poor clinical progression, may suggest inadequate dosing.

- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information

ADVERSE EFFECTS

- **Common:**
  - **Gastrointestinal:** diarrhoea, nausea, vomiting, abnormal (metallic) taste
  - **Neurological:** headache
  - **Hepatic:** transient increases in LFTS
  - **Dermatological:** urticaria, rash

- **Serious:**
  - **Gastrointestinal:** abdominal cramping
  - **Metabolic:** lactic acidosis
  - **Myelosuppression:** thrombocytopenia occurs more commonly on a dosing of 600mg twice a day (licensed dose for bacterial infections). This tends to occur within 7-21 days of therapy. At the lower dose of 600mg once a day it appears to be less common (based on experience from MDRTB). However, it should be monitored and reviewed.
  - **Neurological:** peripheral neuropathy, serotonin syndrome
  - **Ophthalmic:** optic neuropathy – this tends to be non-reversible.
  - **Dermatological:** rare – Bullous disorders such as Stevens-Johnson syndrome & toxic epidermal necrolysis

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- **FBC:** Check at baseline, then every two weeks for one month, then monthly.
- **Lactate:** consider measuring a lactate in those with symptoms of lactic acidosis such as

nausea, vomiting, weight loss, hyperventilation and tachypnea. If elevated and symptoms persist reconsider use of this agent within regimen.
- **Peripheral neuropathy:** patients should be asked at each review (and encouraged to self-report) about any symptoms of a peripheral neuropathy. Clinical examination should be performed to detect signs of a peripheral neuropathy. Nerve conduction studies should be arranged if any signs or symptoms of a peripheral neuropathy.
- **Visual acuity & colour discrimination:** patients should be asked at each review (and encouraged to self-report) about any changes to vision. Consider performing visual acuity and colour discrimination testing (Snellen & Ishihara charts) every month. Refer to ophthalmology if necessary and /or an optic neuritis is suspected

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced drug interactions are expected with linezolid
- Of note clarithromycin increases linezolid serum levels with risk of toxicity.
- Patients should avoid consuming large amounts of tyramine rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products).
- Linezolid should not be given with another monoaimine oxidase inhibitors (MAOI) or within 2 weeks of stopping another MAOI.
- The data on administration of linezolid with selective serotonin reuptake inhibitors (SSRI's) is evolving. Whilst this is a contra-indication, there is a growing evidence base to say these can be administered safely on a case/ case basis. The associated risks of developing serotonin syndrome are perceived to be relatively low with very small number of cases identified in the literature. Pragmatic practice allows for linezolid use in patients on no more than one serotonergic agent. *(ICHNT ARC position statement April 2023)*

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications:**
  - **Hypersensitivity:** to linezolid
  - **Mono-amine oxidase inhibitors:** linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any such medicinal product.
  - Avoid in patients with: uncontrolled hypertension, phaechromocytoma, carcinoid tumour, thyrotoxicosis, bipolar, depression, schizophrenia or acute confusional states
  - Patients taking any of the following medications: serotonin re-uptake inhibitors (see above section), tricyclic antidepressants (see above section), serotonin 5-HT_1 receptor agonists (triptans) (see above section), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.
- **Cautions**

- **Pregnancy & Breastfeeding**
- **Food**: avoid~~:~~ consumption of large amounts of tyramine rich foods
- **Neurological**: use with caution in people with epilepsy/ history of seizures: Increased risk of convulsions
- **Peripheral neuropathy**: use with caution in people with pre-existing peripheral neuropathy of Grade 3–4
- **Optic neuropathy**: Patients should be advised to report symptoms of visual impairment.

NTM Network UK
Non-tuberculous mycobacteria

MINOCYCLINE

*Please note **MINOCYCLINE** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults**: 100mg twice a day (oral)
- **Children (12–17years):** 100mg twice daily (oral). Note: limited data on evidence for dosing in NTM. These doses are based on minocycline dosing for susceptible infections in the latest BNF for children, March 2023 update. In children with CF, doses of 2mg/kg/dose once daily (maximum 200mg) have been recommended.
    - Contraindicated in children under 12 years (deposition in growing bone and teeth, by binding to calcium, causes staining and occasionally dental hypoplasia)

PATIENT COUNSELLING

- To reduce the risk of ulceration and oesophageal irritation minocycline preparations should be swallowed whole, with plenty of liquid, and whilst in an upright sitting or standing position.
- Do not take indigestion remedies, or medicines containing iron or zinc, 2 hours before or after you take this medicine
- Protect skin from sunlight and wear sunscreen even on a bright but cloudy day. Do not use sunbeds. Discontinue therapy at the first sign of skin discomfort
- Space the doses evenly throughout the day. Keep taking this medicine until the course is finished, unless you are told to stop
- Report any sudden onset breathing difficulties, as there have been cases of breathing difficulties including dyspnoea/breathlessness, bronchospasm, exacerbation of asthma, pulmonary eosinophilia and pneumonitis with minocycline use.
- Hyperpigmentation has been reported with long term treatment, and this should be reported to your doctor. This is generally reversible on cessation of therapy.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
    - Minocycline is readily absorbed from the gastrointestinal tract.
    - Absorption is reduced by the concomitant administration of iron salts or antacids containing calcium, magnesium or aluminium salts.
- **Distribution:**
    - Minocycline is more lipid soluble than doxycycline.
    - It is widely distributed in body tissues and fluids. High concentrations are achieved in the hepatobiliary tract, lungs, sinuses and tonsils, as well as in tears, saliva, and sputum.
    - Protein binding is approximately 75%.
- **Metabolism:**
    - Undergoes some hepatic metabolism.
- **Excretion:**
    - Approximately one third of the unchanged drug appears in the urine and two thirds in the faeces.
- **Cmax:**
    - 1 - 4mg/L
- **Tmax:**
    - Tablet: 1 to 3 hours; Modified-release tablet: 3.5 to 4 hours

- **Half-life:**
  - 11 - 23 hours

PREPARATIONS

- **Oral**: 50mg, 100mg tablets, 100mg modified release capsules

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured

ADVERSE EFFECTS

- **Common**
  - **Dermatological**: photosensitivity, rash, angioedema
  - **Gastrointestinal**: nausea, vomiting, diarrhoea, dysphagia
  - **Neurological**: dizziness, headache
  - **Immunological**: hypersensitivity

- **Serious**
  - **Cardiac**: pericarditis (rare)
  - **Dermatological**: exfoliative dermatitis, erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis, photosensitivity skin reactions, photo-onycholysis, skin hyperpigmentation, drug reaction with eosinophilia and systemic symptoms (DRESS)
  - **Gastrointestinal**: oesophagitis and oesophageal ulcerations (take minocycline with plenty of water, during meals while sitting or standing)
  - **Haematological**: haemolytic anaemia, thrombocytopaenia, pancytopenia, neutropenia, eosinophilia, leukopenia, agranulocytosis
  - **Hepatotoxic**: hepatitis, jaundice, hepatic failure and pancreatitis
  - **Immunological**: anaphylaxis, lupus-like syndrome, auto-immune hepatotoxicity
  - **Infections**: pseudomembranous colitis
  - **Neurological**: intracranial hypertension in juveniles and adults, convulsions, bulging fontanelles in infants
  - **Renal**: renal dysfunction (lower risk with doxycycline than with other tetracyclines)
  - **Respiratory**: pulmonary infiltration, pulmonary eosinophilia, exacerbation of asthma, bronchospasm

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

Tests as per generic NTM drug monitoring guidelines.

INTERACTIONS

- **Aluminium**: reduced absorption of minocycline (take minocycline at least 2 hours before or after aluminium-containing preparations)
- **Anticoagulants**: prolonged prothrombin time in patients taking warfarin (monitor INR and

reduce warfarin dose)
- **Calcium**: reduced absorption of minocycline (take minocycline at least 2 hours before or after calcium-containing preparations)
- **Contraceptives**: both can induce hyperpigmentation.
- **Iron**: reduced absorption of minocycline (take minocycline at least 2 hours before or after iron-containing preparations)
- **Lithium**: case reports of increased serum lithium levels/increased risk of lithium toxicity (monitor levels)
- **Magnesium**: reduced absorption of minocycline (take minocycline at least 2 hours before or after magnesium-containing preparations)
- **Retinoids**: (e.g. acitretin, isotretinoin): risk of pseudotumour cerebri (benign intracranial hypertension); avoid use
- **Zinc**: reduced absorption of minocycline (take minocycline at least 2 hours before or after zinc-containing preparations).

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to minocycline, or to other tetracyclines
  - **Children under 12 years** (due to risks of permanent teeth discolouration and enamel hypoplasia)
  - **Pregnancy and breastfeeding**
  - **Systemic lupus erythematosus**: risk of exacerbation
  - **Renal**: complete renal failure

- **Cautions:**
  - **Sunlight**: avoid direct exposure to either extensive sunlight or UV irradiation (photosensitivity risk)
  - **Hepatic** impairment and patients using other potentially hepatotoxic drugs, including alcohol
  - **Myasthenia gravis** (potential for weak neuromuscular blockade)
  - **Galactose intolerance**: minocycline contains lactose and sunset yellow. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. Sunset yellow may cause allergic reactions.

NTM Network UK
Non-tuberculous mycobacteria

MOXIFLOXACIN

*Please note **MOXIFLOXACIN** is not licensed for the treatment of NTM in the UK*

DOSAGE

- **Adults:** 400mg once a day (oral or intravenous).
- **Children:** 10-15mg/kg once a day; max 400mg daily (oral).

Note: limited data on evidence for dosing in NTM. These doses are based on MDR-TB dosing based on WHO 2022 and Sentinel 2022 updates

- Situations where dosage adjustments may be required,
  - **Renal disease:** no dose adjustment necessary.
  - **Hepatic disease:** no dose adjustment necessary. However, manufacturer advises avoid in severe impairment or increased transaminases (5 times upper limit of normal).
  - **Obesity:** limited data; no dose adjustment necessary.

PATIENT COUNSELLING

- Can be taken with or without food. Swallow this medicine whole. Do not chew or crush
- Do not take milk, indigestion remedies or medicines containing iron or zinc, 2 hours before or after you take this medicine.
- Side effects may include nausea, diarrhoea, vomiting, constipation, abdominal pain, dyspepsia, headache, or insomnia.
- Avoid direct exposure to either extensive sunlight or UV irradiation during treatment
- Tendon damage (including rupture) has been reported rarely in patients receiving quinolones therefore stop treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling. The MHRA has produced an advice sheet, which should be provided to patients and their carers.
- Due to the small increased risk of aortic aneurysm and dissection, seek immediate medical attention if sudden-onset severe abdominal, chest, or back pain develops.
- Seek immediate medical attention if experience a rapid onset of shortness of breath (especially when lying down flat in bed), swelling of the ankles, feet, or abdomen, or new-onset heart palpitations.
- Nerve damage (neuropathy) is a rare side effect. Report any abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in your body, especially in the legs or arms, or difficulty walking.
- Psychiatric reactions are a rare side effect. Report any symptoms of severe tiredness, depressed mood, anxiety, or problems with your memory or severe problems sleeping
- Due to neurological side effects, moxifloxacin may impair performance of skilled tasks (e.g. driving and operating machinery)
- Patients with diabetes should monitor for hyperglycaemia or hypoglycaemia and report any concerns with their glycaemic control.

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Moxifloxacin is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration.
  - The bioavailability is approximately 91%.
- **Distribution:**

  - Widely distributed into body tissues, with good central nervous system (CNS) penetration.
  - Moxifloxacin is 30-50% bound to plasma proteins.
- **Metabolism:**
  - Moxifloxacin undergoes hepatic metabolism, mainly via sulfate and glucuronide conjugation.
  - The CYP450 pathway does not appear to be involved in the metabolism of moxifloxacin.
- **Excretion:**
  - Excreted in the urine and the faeces as unchanged drug and as metabolites; the sulfate conjugate mainly in the faeces and the glucuronide exclusively in the urine.
- **Cmax:**
  - 3.1mg/L after a single 400mg oral dose, and 3.2mg/L at steady state
- **Tmax:**
  - 0.5 - 4 hours
- **Half-life:**
  - 12 hours

PREPARATIONS

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

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Known or suspected malabsorption.
  - Poor treatment response.
- **Target Level:**
  - Trough (pre dose): 0.3 - 0.7mg/L
  - Peak (post dose): 3 - 5mg/L
- **Timing of Sample:**
  - Trough: immediately before a dose is taken. Consider trough levels **only** if suspect delayed absorption
  - Peak: 2 hours post dose. Repeat at 6 hours if suspect delayed absorption.
- **Frequency of Levels:**
  - No need for regular monitoring.
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information

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:** agranulocytosis, aplastic anaemia, haemolytic anaemia, thrombocytopaenia (uncommon).
- **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 central nervous system (CNS) disorders).
- **Renal:** renal impairment (rare).
- **Respiratory:** extrinsic allergic alveolitis (rare).
- **Other:** serum sickness (rare).

This information is not exhaustive. Please discuss with a pharmacist.

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.
- **Calcium and magnesium**: at baseline and repeated if QT prolongation is detected.
- **Blood glucose** should be monitored regularly in patients with diabetes (risk of hypoglycaemia).

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Antacids: reduced absorption of moxifloxacin.
- Anti-arrhythmics: increased risk of ventricular arrhythmias with amiodarone or disopyramide.
- Antidepressants: increased risk of ventricular arrhythmias with tricyclics.
- Antimalarials: increased risk of ventricular arrhythmias with chloroquine, hydroxychloroquine, mefloquine, quinine.
- Antipsychotics: increased risk of ventricular arrhythmias with benperidol, droperidol, haloperidol, phenothiazines, pimozide and zuclopenthixol.
- Antivirals: increased risk of ventricular arrhythmias with saquinavir.
- Beta-blockers: increased risk of ventricular arrhythmias with sotalol.
- Ciclosporin: increased risk of nephropathy.
- Erythromycin: increased risk of ventricular arrhythmias when erythromycin given via intravenous route.
- Iron: reduced absorption of moxifloxacin.
- Non-steroidal anti-inflammatories: possible increased risk of convulsions.
- Pentamidine: increased risk of ventricular arrhythmias.
- Rifampicin: reduced moxifloxacin levels but the clinical relevance of this appears limited
- 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

- **Contra-indications:**
  - **Hypersensitivity:** to moxifloxacin or other quinolones.
  - **Tendon Damage:** rarely reported but damage or rupture may occur within 48 hours of treatment and several months after stopping treatment. Increased risk in patients with a history of tendon disorders related to quinolone use, aged over 60 years, concomitant use of corticosteroids. Cease all quinolone treatment if tendinitis suspected.
  - **Pregnancy:** avoid in pregnancy; animal studies have shown quinolones cause arthropathy.
  - **Breastfeeding:** avoid, present in milk in animal studies.
  - **Children:** moxifloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in NTM with caution; arthropathy has developed in weight-bearing joints of 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.
  - **Glucose-6-phosphate dehydrogenase (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.

NTM Network UK
Non-tuberculous mycobacteria

RIFABUTIN

*Please note **RIFABUTIN** is not licensed for the treatment of NTM in the UK*

DOSAGE

- **Adults**: usual dose is 300mg ONCE a day. Reduce to 150mg once a day when taken with clarithromycin. In non-severe MAC-pulmonary disease, a dose of 300mg three times per week (oral) may be used.
- **Children 12–17 years):** 5mg/kg once a day (oral).
- **Children (1 month – 11 years):** 5mg/kg once a day (limited data).

- Renal impairment: reduce dose if creatinine clearance <30mL/hr; discuss with a pharmacist

PATIENT COUNSELLING

- Swallow capsules whole with or without food.
- Rifabutin colours soft contact lenses permanently and other body secretions red-orange including the urine and possibly the skin.
- Patients or carers should be warned how to recognise signs of a liver disorder, including to seek medical attention if persistent nausea, vomiting, malaise or jaundice develop
- Rifabutin induces hepatic enzymes and can reduce the effectiveness of hormonal contraceptives; alternative family planning options should be offered (e.g. barrier methods such as condoms).
- Report any serious skin rashes

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Rifabutin is rapidly absorbed. Bioavailability is approximately 20%.
- **Distribution:**
  - Rifabutin is widely distributed in the body, with the exception of the brain. Concentrations in lung tissue measured up to 24 hours after dosing were about 5-10 times higher than the plasma levels.
- **Metabolism:**
  - Rifabutin undergoes hepatic metabolism to five different metabolites. The two major metabolites of rifabutin contribute to its antimicrobial activity.
- **Excretion:**
  - Rifabutin and its metabolites are eliminated in the urine (53%), as well as in the faeces (30%).
- **Cmax:**
  - 0.4 - 0.7mg/L (dose range 300-600mg).
- **Tmax:**
  - 2-4 hours.
- **Half-life:**
  - 35-40 hours.

PREPARATIONS

- **Oral**: 150mg capsules

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Known or suspected malabsorption
  - Poor treatment response.
  - Useful in cases where co-administered with other agents that have known drug interactions (such as clarithromycin, antifungal agents and antiretroviral treatments).
- **Target Level:**
  - Trough (pre dose): <0.1mg/L
  - Peak (post dose): 0.45 – 0.9mg/L
- **Timing of Sample:**
  - Trough: immediately before a dose is taken
  - Peak: 3-hour post dose level. In situations with suspected malabsorption, take 3 post dose samples 1h, 2h and 4h after oral administration
- **Frequency of Levels:**
  - Drug levels need not be routinely measured.
- **Suggested actions:**
  - If low post-dose levels, consider dose increase.
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information

ADVERSE EFFECTS

- **Common**
  - Reddish discolouration of urine, sweat, sputum, tears
  - Haematological: leucopenia
  - Gastrointestinal: anorexia, nausea, vomiting, heartburn
  - Hepatic: transient increases in LFTs
  - Ophthalmic: uveitis
  - Immunological: rash.
  - Musculoskeletal: myalgia
  - General: pyrexia.
- **Serious**
  - Haematological: pancytopenia, agranulocytosis, neutropenia, thrombocytopenia
  - Immunological: hypersensitivity, bronchospasm, severe cutaneous reactions (e.g. Steven-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms and acute generalised exanthematous pustulosis)
  - Ophthalmic: uveitis
  - Hepatic: liver enzymes increased, jaundice.

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- Uveitis is more common when given with interacting drugs such as clarithromycin or fluconazole. In such patients this symptom should be monitored for closely and referred to an ophthalmologist promptly if this event occurs.
- If a patient develops a rash, they should be closely monitored and suspected drug(s) discontinued. It can be difficult to identify the cause in a multi-drug regimen.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- Antibiotics: increased levels of rifabutin with clarithromycin, erythromycin (reduce rifabutin dose). Azithromycin increase risk of neutropenia.
- Anticoagulants: reduced INR with warfarin and other coumarins, increased dose and monitoring required
- Antiepileptics: reduced concentration of carbamazepine and phenytoin, dose adjustment required (increased risk of seizures)
- Antifungals: increased serum concentration of rifabutin and reduced antifungal levels with fluconazole, itraconazole, posaconazole, voriconazole. If required consider monitoring levels of antifungal and possibly rifabutin; reduced dose of rifabutin and increased dose of antifungal may be required
- Antipsychotics: reduced concentration of aripiprazole
- Antivirals: amprenavir, fosamprenavir/ritonavir, indinavir, lopinavir/ritonavir, saquinavir, ritonavir, atazanavir; increased levels of rifabutin and possibly reduced levels of antiretrovirals; consult with HIV physician prior to commencing treatment https://www.hiv-druginteractions.org/checker
- CFTR modulators: ivacaftor; reduced ivacaftor levels – avoid
- Contraceptives and HRT: reduced levels of oestrogens and progestogens (reduced contraceptive effect)
- Corticosteroids: reduced levels of corticosteroid (reduced effect)
- Immunosuppressants: reduced concentration of sirolimus and tacrolimus
- Methadone: reduced concentrations, risk of withdrawal symptoms

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity** to the active substance or other rifamycins;
  - **Pregnancy and breastfeeding**: avoid due to limited information
- **Cautions:**
  - **Liver impairment**: increased risk of liver toxicity;
  - **Renal impairment**: reduce dose

NTM Network UK
Non-tuberculous mycobacteria

RIFAMPICIN

*Please note **RIFAMPICIN** is not licensed for the treatment of NTM in the UK*

DOSAGE

- **Adults**:
  - <50kg: 450mg once a day (oral or intravenous)
  - 50kg+: 600mg once a day (oral or intravenous)
  - In non-severe MAC-pulmonary disease, a dose of 600mg three times per week (oral) may be used.
- **Children**:
  - 15 mg/kg (max 450mg if <50kg; 600mg if 50kg+) once a day (oral or intravenous)
  - Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of capsule.

PATIENT COUNSELLING

- Rifampicin should be taken 30–60 min before food, or 2 hours after food.
- Rifampicin colours soft contact lenses permanently and other body secretions red-orange including the urine and possibly the skin.
- Patients or carers should be warned how to recognise signs of a liver disorder, including to seek medical attention if persistent nausea, vomiting, malaise or jaundice develop
- Rifampicin induces hepatic enzymes and can reduce the effectiveness of hormonal contraceptives; alternative family planning options should be offered (e.g. barrier methods such as condoms).

NTM Treatment Patient Information Leaflets are available from NTM Patient Care UK:
https://www.ntmpatientcare.uk/coping-with-the-medicines

PHARMACOKINETICS

- **Absorption:**
  - Rifampicin is readily absorbed from the gastrointestinal tract.
  - Bioavailability is 70%.
  - Absorption of rifampicin is reduced when the drug is ingested with food
- **Distribution:**
  - Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid (CSF).
  - The ratio of CSF to blood level in people with inflamed meninges is 25%.
  - Rifampicin is about 80% protein bound.
- **Metabolism:**
  - Rifampicin is rapidly eliminated in the bile and an enterohepatic circulation ensues.
  - During enterohepatic circulation, rifampicin undergoes progressive deacetylation to an active metabolite, so that nearly all the drug in the bile is in this form in about 6 hours.
  - Intestinal reabsorption is reduced by deacetylation and elimination is facilitated.
- **Excretion:**
  - The majority of the drug is excreted in the faeces, but up to 30% is excreted in the urine, with about half of this being unchanged drug.
- **Cmax:**
  - 10mg/L
- **Tmax:**
  - 2 - 4 hours
- **Half-life:**

- 2.5 - 3 hours.

PREPARATIONS

- **Parenteral**: 600mg powder for reconstitution.
- **Oral**: 150mg and 300mg capsules, 100mg/5mL oral suspension

DRUG LEVEL MONITORING

- **Indications for monitoring:**
  - Known or suspected malabsorption
  - Poor treatment response.
- **Target Level:**
  - Peak (post dose): 8-24mg/L
- **Timing of Sample:**
  - Peak: 2 hours post oral dose. Repeat at 6 hours post dose if delayed absorption is suspected. OR 1 hour post intravenous dose
- **Frequency of Levels:**
  - Drug levels need not be routinely measured.
- **Suggested actions:**
  - If serum rifampicin levels are low in the context of poor treatment response or known/suspected malabsorption, increase dose cautiously, and repeat levels after 3-5 days.
- **Availability of TDM:**
  - North Bristol NHS Trust Antimicrobial Reference Laboratory. https://www.nbt.nhs.uk/severn-pathology/requesting/test-information

ADVERSE EFFECTS

- **Common**
  - Reddish discolouration of urine, sweat, sputum, tears
  - Flu-like syndrome
  - Gastrointestinal: nausea, vomiting
  - Haematologic: thrombocytopenia with or without purpura (usually associated with intermittent therapy). Reversible after discontinuing rifampicin. Note: it is not usually recommended to re-introduce rifampicin after an episode of significant thrombocytopenia
  - Hepatic: transient increases in transaminases and bilirubin
  - Neurologic: headache, dizziness
- **Serious**
  - Haematological: agranulocytosis (rare), haemolytic anaemia (rare, usually intermittent therapy), thrombocytopaenia (rare, usually high-dose/intermittent therapy)
  - Hepatic: hepatotoxicity (rare)
  - Renal: nephrotoxicity (rare).

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

Tests as per generic NTM drug monitoring guidelines.

INTERACTIONS

- **Analgesics**: accelerated metabolism of opiates, resulting in reduced effect (e.g. alfentanyl, codeine, fentanyl, methadone, morphine and possibly oxycodone).
- **Antacids**: reduced absorption of rifampicin.
- **Anti-arrhythmics**: accelerated metabolism of disopyramide, propafenone.
- **Antibacterials**: reduced plasma concentrations of chloramphenicol, clarithromycin, dapsone, doxycycline, linezolid, moxifloxacin, trimethoprim.
- **Anticoagulants**: reduced plasma concentration of apixaban, dabigatran and rivaroxaban; accelerated metabolism of coumarins (e.g. warfarin).
- **Anti-diabetics**: accelerated metabolism of tolbutamide and sulfonylureas (reduced effect); reduced effect of linagliptan, netaglinide and repaglinide.
- **Antiepileptics**: reduced plasma concentration of lamotrigine and phenytoin; phenobarbital possibly reduces plasma concentration of rifampicin.
- **Antifibrotics**: reduced exposure to nintedanib and pirfenidone; avoid concomitant treatment.
- **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). Consult with HIV physician prior to commencing treatment. Interactions can be checked via https://www.hiv-druginteractions.org/checker
- **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.
- **CFTR modulators**: reduced plasma concentration of ivacaftor, tezacaftor, elexacaftor (co-administration is not recommended)
- **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). Intrauterine contraception and depot medroxyprogesterone acetate (either intramuscular or subcutaneous) are appropriate options
- **Corticosteroids**: accelerated metabolism of corticosteroids (reduced effect). Dose of corticosteroids should be doubled
- **Diuretics**: reduced plasma concentration of eplerenone (avoid concomitant use).
- **Hormone Replacement Therapy (HRT)**: rifampicin would be expected to reduce the efficacy of HRT.
- **Methadone**: reduced concentrations, risk of withdrawal symptoms. Methadone doses should be adjusted once rifampicin is introduced or ceased.
- **Mycophenolate**: reduced plasma concentration of active metabolite of mycophenolate.
- **P-aminosalicylic acid**: reduced absorption of rifamycins. Give 8-12 hours apart.
- **Ranolazine**: reduced plasma concentration of ranolazine (avoid concomitant use).

- **Sirolimus**: reduced in plasma concentration of sirolimus (monitor sirolimus levels closely and adjust dose).
- **Tacrolimus**: reduced in plasma concentration of tacrolimus (monitor tacrolimus levels closely and adjust dose).
- **Tadalafil**: reduced plasma concentration of tadalafil (avoid concomitant use).
- **Theophylline**: accelerated metabolism of theophylline (reduced plasma concentration).
- **Ticagrelor**: reduced plasma concentration of ticagrelor.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity**: to rifampicin or other rifamycins
  - **Liver disease**: avoid if known chronic liver disease
  - **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.
  - **People at bleeding risk**: rifampicin may cause vitamin K dependent coagulopathy and severe bleeding. Monitoring for coagulopathy is recommended for people at risk.
  - **Pregnancy and breastfeeding**: manufacturer advises that it may be considered for use if benefits to the mother outweigh potential risks to the child.

NTM Network UK
Non-tuberculous mycobacteria

TIGECYCLINE

*Please note **TIGECYCLINE** is not licensed for the treatment of NTM in the UK.*

DOSAGE

- **Adults**: 100mg loading dose, then 50mg once or twice daily. Many experts recommend once daily dosing due to the high rate of drug-related adverse reactions associated with twice-daily dosing
- **Children**:
  - 12–18 years: 100mg loading dose, then 50mg twice daily
  - 8–11 years: 1.2mg/kg twice daily (maximum 50mg twice daily)
  - <8 years: No data available. The safety and efficacy of tigecycline has not been established and may cause teeth discolouration in children aged under 8 years.
- **Elderly**: No dosage adjustment is necessary in elderly patients

- **Renal impairment:** no dosage adjustment required.
- **Hepatic impairment**: no dosage adjustment required in mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). Reduce dose in severe hepatic impairment (Child Pugh C)

PATIENT COUNSELLING

- Severe nausea and vomiting are common. Consider prescribing and optimising regular anti-emetics to support the patient to tolerate treatment.
- Dizziness may occur and this may have an effect on driving and use of machines.
- Increased risk of hepatotoxicity when alcohol is consumed with tigecycline.
- Oral contraceptives may be less effective when taken with tigecycline. It is recommended to use another form of birth control (e.g. barrier method) whilst on this antibiotic.
- Report immediately if you develop severe abdominal pain, or nausea and vomiting, as these may be symptoms of acute pancreatitis.

PHARMACOKINETICS

- **Absorption:**
  - 100% bioavailability with intravenous administration.
- **Distribution:**
  - Plasma protein binding: 71-89%
  - Readily distributes to tissues
  - Unknown if crosses the human blood-brain barrier
- **Metabolism:**
  - An average of <20% of tigecycline is metabolised before excretion
- **Excretion:**
  - 59% of tigecycline is excreted via biliary/faecal excretion and 33% via urine. Biliary excretion being the primary route of elimination of unchanged tigecycline.
- **Cmax:**
  - 866 ± 233ng/ml for 30-minute infusions and 634 ± 97ng/mL for 60-minute infusions.
- **Tmax:**
  - 30 minutes
- **Half-life:**
  - 42 hours

PREPARATIONS

- **Parenteral**: 50mg powder for solution for infusion.

DRUG LEVEL MONITORING

- Drug levels cannot currently be performed in the UK

ADVERSE EFFECTS

- **Common**
  - **Dermatological**: pruritus, rash, impaired healing, injection site reaction
  - **Gastrointestinal**: nausea, vomiting, diarrhoea, abdominal, pain, dyspepsia, anorexia
  - **Haematological**: prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)
  - **Hepatic**: elevated LFTs (aspartate transferase (AST), alanine transaminase (ALT), bilirubin)
  - **Infections**: sepsis/septic shock, pneumonia, abscess, infections
  - **Investigations**: elevated amylase, elevated blood urea nitrogen
  - **Metabolic**: hypoglycaemia, hypoproteinaemia
  - **Neurological**: dizziness, headache
  - **Vascular**: phlebitis
- **Serious**
  - **Dermatological**: severe skin reactions, including Stevens-Johnson syndrome, photosensitivity
  - **Haematological**: thrombocytopaenia
  - **Hepatic**: hepatic failure, acute pancreatitis
  - **Immunological**: anaphylaxis
  - **Infections**: sepsis/septic shock, pneumonia, abscess, infections, pseudomembranous colitis
  - **Neurological**: benign intracranial hypertension.
- **Overdose**
  - No specific information is available on the treatment of overdosage.
  - Intravenous administration of tigecycline at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting.

This information is not exhaustive. Please discuss with a pharmacist.

ADVERSE EFFECTS: MONITORING

- LFTs, FBC, clotting and amylase should be monitored at baseline and regularly while on treatment.

Blood toxicity monitoring tests (full blood count (FBC), urea & electrolytes (U&Es), liver function tests (LFTs)) should be performed intermittently throughout antibiotic treatment (unless more specific advice is outlined above).

INTERACTIONS

- **Anticoagulants**: prolonged prothrombin time in patients taking anticoagulants, including warfarin (monitor INR and adjust dose)
- **Ciclosporin**: increased ciclosporin serum concentrations may occur (monitor ciclosporin levels

closely and adjust dose)
- **Retinoids**: increased risk of benign intracranial hypertension, manufacturer advises avoid.
- **Tacrolimus**: increased tacrolimus serum concentrations may occur (monitor tacrolimus levels closely and adjust dose).
- **Typhoid vaccine**: tigecycline may reduce the efficacy of the oral typhoid vaccine. Advise to stop antibiotics 3 days before and after vaccine administration.
- Increased risk of hepatotoxicity: use in caution and monitor LFTs closely when tigecycline is given with other drugs which can also cause hepatotoxicity.

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

CONTRA-INDICATIONS & CAUTIONS

- **Contra-indications**:
  - **Hypersensitivity**: to tigecycline or to tetracyclines
  - **Paediatric patients** aged <8 years
- **Cautions:**
  - **Pregnancy**: 1st trimester: risk of reproductive toxicity and skeletal development defects in animal studies. 2nd or 3rd trimester: risk of child's teeth discolouration and potential maternal hepatotoxicity. Only to be used if the patient's clinical condition requires treatment with tigecycline.
  - **Breastfeeding**: manufacturer advises avoid; present in milk in animal studies.
  - **Hepatological**: use in patients with pre-existing liver conditions; manufacturer advises to monitor closely.
  - **Haematological**: caution in patients taking anticoagulants, tigecycline may prolong prothrombin time (PT) and activated partial thromboplastin time (aPTT).
  - **Pancreatitis**: an uncommon side effect of tigecycline, consider as a diagnosis in patients on tigecycline with abdominal pain which usually develops after at least one week of treatment. Discontinue tigecycline if pancreatitis develops.
  - **Pseudomembranous colitis**: reported in nearly all antibacterial agents. Consider as a diagnosis in patients on tigecycline who present with diarrhoea during or after administration.

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List of Contributors

- Dr Toby GD Capstick, Consultant Pharmacist - Respiratory Medicine, Leeds Teaching Hospitals NHS Trust (Joint Lead)
- Christabelle Chen, Lead Respiratory Pharmacist, Barts Health NHS Trust (Joint Lead)
- Jessica Gadsby, Advance Specialist Pharmacist – Adult Cystic Fibrosis, University Hospitals of Leicester NHS Trust (Joint Lead)
- Josie Cunningham, Lead for quality improvement in cystic fibrosis Frimley Health NHS Trust
- Elaine Bowman, Lead Respiratory Pharmacist - Respiratory Medicine. Royal Brompton & Harefield NHS Foundation Trust
- Annette Clarkson, Lead Pharmacist antimicrobials, OPAT and infection control, Nottingham
- Arianwen Denham, North Bristol NHS Trust
- Mark Gilchrist, Consultant Pharmacist Infectious Diseases, Imperial College Healthcare NHS Trust
- Sarah Hackney, Advanced Clinical Pharmacist - Infectious Diseases & Antimicrobial Stewardship, Leeds Teaching Hospitals NHS Trust
- Kirsteen Hill, Antimicrobial/HIV Pharmacist. NHS Tayside, Ninewells Hospital
- Fiona Lynch, Infectious Diseases Pharmacist, Wythenshawe Hospital, Manchester
- Douglas McCabe, Lead Respiratory & Adult Cystic Fibrosis Pharmacist. Western General Hospital, NHS Lothian
- Dr John E Pearl, Department of Respiratory Sciences, University of Leicester
- Ceri Phillips, Consultant Pharmacist – Antimicrobials. Aneurin Bevan University Health Board
- Lauren Rose, Antimicrobials and Infection Control. Nottingham University Hospitals NHS Trust