Medicine Guideline

Bedaquiline fumurate for resistant pulmonary tuberculosis

Health
South Eastern Sydney
Local Health District

Areas where Protocol/Guideline applicable	Inpatient ward areas and outpatients seen by Respiratory tuberculosis (TB) clinic or Infectious Disease (ID) clinic
Authorised Prescribers:	Respiratory specialist, Infectious Diseases specialist This medication will require an SAS form (Category A) to be completed for the entire course of therapy
Indication for use	Multidrug-resistant pulmonary tuberculosis (MDR-TB) or extensively drug resistant pulmonary tuberculosis (XDR-TB)
Clinical condition Patient selection: Inclusion criteria	Pulmonary tuberculosis in adults (≥5 years) – resistant to standard therapy but sensitive to bedaquiline. Used in combination with at least 2 other drugs to which the patient's MDR-TB isolate has been shown to be susceptible.
Proposed Place in Therapy	Used as part of combination first line therapy for multi-drug resistant or extensively drug resistant pulmonary tuberculosis.
Adjunctive Therapy	Pretomanid, Linezolid, Moxifloxacin
Contra-indications	Known hypersensitivity. Men should agree to use highly effective method of birth control and not to donate sperm during treatment and for 3 months after receiving the last dose Children < 5 year of age
Precautions	An increased risk of death was observed in the bedaquiline treatment group in one placebo-controlled trial. The imbalance of deaths is unexplained. Should only be used when an effective treatment regimen cannot otherwise be provided. QT prolongation – see monitoring requirements and caution when used with other QT prolonging medications (e.g. fluoroquinolones, macrolides, clofazimine). Caution if history of: Torsade de Points, congenital long QT syndrome, hypothyroidism and bradyarrhythmia's, uncompensated heart failure. Patients should be advised to avoid alcohol while on therapy Pregnancy and breastfeeding Severe hepatic impairment
Important Drug Interactions	Bedaquiline is metabolized by CYP3A4. Therapeutic effect may be reduced when administered with inducers of CYP3A4. Avoid concomitant administration with strong CYP 3A4 inducers (e.g. rifampicin)

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	Therapeutic exposure to bedaquiline may increase with strong CYP3A4 inhibitors and increase risk of adverse reaction. Avoid use of strong CYP3A4 inhibitors for more than 14 consecutive days while on bedaquiline unless benefit of treatment outweighs the risk. Dose modification of bedaquiline may be required when used together with lopinavir/ritonavir-containing regimens used to treat HIV.
Dosage (Include dosage adjustment for specific patient groups)	**Adult dose:** Weeks 1 to 2: 400mg orally, once daily with food Weeks 3 to 24: 200mg orally, three times per week with food (with at least 48 hours between doses) (for a total dose of 600mg per week) Alternative regimen:200mg orally once daily with food for 8 weeks, followed by 100mg once daily with food for 18 weeks. **Paediatric dose (≥5 years):** **15 to <30kg:** Week 1 to 2: 200mg PO once daily with food Week 3 to 24: 100mg PO three times weekly with at least 48 hours between doses (for a total dose of 300mg per week) **≥30 kg:** Week 1 & 2: 400mg PO once daily with food Week 3 to 24: 200mg PO three times weekly with at least 48 hours between doses (for a total dose of 600mg per week) *(Or as otherwise prescribed according to the best available evidence at the time of prescribing.)*
Duration of therapy	The total duration of therapy is usually 26 weeks (6 months) but may be extended up to 39 weeks (9 months), depending on the regimen used.
Prescribing Instructions	**Inpatients** Bedaquiline must be prescribed on the eMR, eRIC, or in Mosaiq/ARIA. **Outpatients** Bedaquiline must be prescribed on an approved SESLHD internal prescription.
Administration Instructions	Orally with food

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Monitoring requirements	Baseline ECG and ECG at least at 2, 12 and 24 weeks after starting treatment. Consider weekly monitoring if concurrent use of other drugs that prolong QTc (e.g. fluoroquinolone, macrolide, or clofazimine) EUC & CMP - Serum potassium, calcium, magnesium at baseline and corrected if abnormal. Follow up monitoring of electrolytes if QT prolongation is detected. Monitor for symptoms of hepatic-related adverse effects and ALT, AST, alkaline phosphatase, bilirubin at baseline, monthly while on treatment and as needed. Monitor weekly for nausea, headache, haemoptysis, chest pain, arthralgia and rash.
Management of Complications	**QT prolongation** Discontinue if patient develops clinically significant ventricular arrhythmia, QTc interval of >500ms (confirmed by repeat ECG) If syncope occurs obtain and ECG to assess for QT prolongation **Hepatic complications** Increase of serum aminotransferases to >3x ULN should be followed by repeat testing within 48 hours. Test for viral hepatitis and discontinue other hepatotoxic medications. Discontinue bedaquiline if: - Aminotransferase elevations are accompanied by total bilirubin elevation >2x Upper limit normal (ULN) - Aminotransferase elevations are >8x ULN - Aminotransferase elevations are >5x ULN & persist beyond 2 weeks
Basis of Protocol/Guideline: (including sources of evidence, references)	Provisional CDC Guidelines for the Use and safety monitoring of bedaquiline fumarate for the treatment of multidrug-resistant tuberculosis. MMWR, 2013; 62(9); 1-12. SIRTURO PI (accessed via UpToDate) Sanford Guide 54th Ed. 2024. Micromedex 2024 Nahid P et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. AM J Respir Crit Care Med 2019; 200(10): e93-e142. Conradie F, Diacon AH, Ngubane N, et al; Nix-TB Trial Team. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382(10):893-902. doi:10.1056/NEJMoa1901814 Francesca Conradie, Tatevik R. Bagdasaryan, Sergey Borisov, et al. for the ZeNix Trial Team, Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis, N Engl J Med 2022;387:810-823, DOI: 10.1056/NEJMoa2119430

	Bern-Thomas Nyang'wa, Catherine Berry, Emil Kazounis, et al. for the TB-PRACTECAL Study Collaborators, A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis, N Engl J Med 2022;387:2331-2343, DOI: 10.1056/NEJMoa21171 WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2022 Margreke J.E. Brill, Elin M. Svensson, Mishal Pandie, et al., Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug-resistant tuberculosis, International Journal of Antimicrobial Agents, Volume 49, Issue 2, 2017, Pages 212-217, doi.org/10.1016/j.ijantimicag.2016.10.020.
Groups consulted in development of this guideline (previous prescribing protocol)	AMS pharmacist, ID Department, Respiratory/Tuberculosis Specialist, Antimicrobial Stewardship Committee for Prince of Wales Hospital and St George Hospital, Guidance Management Committee

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GOVERNANCE	
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