Bedaquiline

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.5. Antituberculosis medicines

EMLc | ATC codes: J04AK05

Indication	Multi-drug resistant Mycobacterium tuberculosis ICD11 code: ML32.00
INN	Bedaquiline
Medicine type	Chemical agent
List type	Complementary (EML) (EMLc)
Additional notes	Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control.
Formulations	Oral > Solid: 100 mg tablet ; 20 mg tablet (EMLc)
EML status history	First added in 2015 (TRS 994) Changed in 2019 (TRS 1021) Changed in 2021 (TRS 1035) Changed in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Bedaquiline
DrugBank	Bedaquiline

Expert Committee recommendation

The Expert Committee recommended the removal of the age restriction from the listing of bedaquiline on the EML and EMLc, consistent with the recommendations for use of bedaquiline in current WHO guidelines for management of tuberculosis in children and adolescents.

Background

Bedaquiline tablets for use in the treatment of multidrug-resistant tuberculosis (MDR-TB) have been listed on the EML and EMLc since 2015 and 2019, respectively. When bedaquiline was added to the EMLc in 2019, an age limit of ≥ 6 years was included, in line with WHO guideline recommendations at the time. The age limit was amended to ≥ 5 years in 2021, in line with updated WHO guidelines.

Public health relevance

The public health relevance of effective treatments for MDR-TB is well established. In 2021, the estimated incidence of tuberculosis disease in children younger than 15 years was 1.15 million (1). While the exact burden of MDR-TB in children is still unknown, more than 30 000 cases are estimated to occur globally each year (2,3). In 2021, 5506 children and young adolescents (0–14 years) were initiated on second-line treatment for MDR-TB or rifampicin-resistant tuberculosis (RR-TB).

Benefits

A descriptive analysis of data from a paediatric MDR-TB/RR-TB individual patient dataset included 40 children younger than 6 years and 68 children aged 6–12 years who received bedaquiline off-label under programmatic conditions. In a matched analysis, bedaquiline was associated with significantly shorter treatment duration and a lower adjusted odds ratio (OR) of injectable tuberculosis drug use (4). The certainty of evidence was very low of no statistically significant difference in successful treatment outcomes between children younger than 6 years receiving an all-oral bedaquiline-based regimen compared with children not receiving bedaquiline (OR 0.94, 95% confidence interval (CI) 0.09 to 10.30). In absolute terms, this represents two fewer treatment successes per 1000 children treated (95% CI 203 fewer to 24 more) (5). Population pharmacokinetic models from two phase II trials of bedaquiline in children – TMC207-C211 (6) and IMPAACT P1108 (7) – suggest that drug exposures observed in adults can be reached in most children receiving bedaquiline, however some dose modification may be necessary for some children depending on age and weight (4).

Harms

The most common adverse effects of bedaquiline include headache, nausea, liver dysfunction, QT interval prolongation and arthralgia. Available interim data from IMPAACT P1108 were based on a small sample size (n = 12) but did not suggest distinct cardiac safety signals with bedaquiline in children 0–6 years compared with cardiac safety reported in adults (4). No children had QT prolongation in any categories of ≥ 60 ms. Three children experienced QT prolongation of between 3 ms and 60 ms. However, the safety review was not complete as not all children enrolled had completed the full course of bedaquiline treatment (24 weeks). At this time, long-term safety and adverse event data are lacking for children younger than 6 years receiving bedaquiline.

Cost / cost effectiveness

Information on the cost and cost–effectiveness of bedaquiline has been presented and considered previously. No new information is available.

WHO guidelines

WHO guidelines for the management of tuberculosis in children and adolescents include a conditional recommendation (very low-certainty evidence) that an all-oral treatment regimen containing bedaquiline may be used in children younger than 6 years with MDR-TB and RR-TB (4).

Availability

Information on the market availability of bedaquiline has been presented and considered previously. No new information is available.

Other considerations

In October 2021, WHO convened an expert consultation on bedaquiline dosing in young children. By accounting for age, body weight and other known covariates, an adult population pharmacokinetic model was used to simulate dose–exposure scenarios for a virtual representative paediatric population. Using these population pharmacokinetic methods and trial-based paediatric bedaquiline pharmacokinetic data, a combined age- and weight-based approach to bedaquiline dosing was developed for children weighting 3 to < 16 kg, and is included in the WHO operational handbook on tuberculosis (8). Bedaquiline is metabolized by CYP3A4, and children younger than 6 months have immature enzyme function resulting in lower bedaquiline clearance. Doses are therefore adjusted based also on age to avoid excessively high bedaquiline concentrations and resultant risk of toxicity.

1. Global tuberculosis report 2022. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/363752, accessed 6 October 2023).
2. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572–9.
3. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. Lancet Infect Dis. 2016;16(10):1193–201.
4. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/352522, accessed 6 October 2023).
5. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. Web Annex 2: GRADE summary of findings tables. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/352508, accessed 6 October 2023).
6. Pharmacokinetic study to evaluate anti-mycobacterial activity of TMC207 in combination with background regimen (BR) of multid

rug resistant tuberculosis (MDR-TB) medications for treatment of children/adolescents pulmonary MDR-TB. ClinicalTrials.gov identifier: NCT02354014. Washington, DC: US National Library of Medicine; 2015 (https://clinicaltrials.gov/ct2/show/NCT02354014, accessed 6 October 2023).
7. Evaluating the pharmacokinetics, safety, and tolerability of bedaquiline in HIV-infected and HIV-uninfected infants, children, and adolescents with multidrug-resistant tuberculosis. ClinicalTrials.gov identifier: NCT02906007. Washington, DC: US National Library of Medicine; 2016 (https://clinicaltrials.gov/ct2/show/NCT02906007, accessed 6 October 2023).
8. WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/352523, accessed 6 October 2023).