



		EMLc	ATC codes: J04AK05
Indication	Multi-drug resistant tuberculous Mycobacterium	ICD11 code: ML32.00	
INN	Bedaquiline		
Medicine type	Chemical agent		
List type	Complementary 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		
EML status history	First added in 2015 (TRS 994) Changed in 2019 (TRS 1021)		
Sex	All		
Age	Also recommended for children		
Age restriction	≥6 years		
Therapeutic equivalence	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 addition of bedaquiline to the complementary list of the EMLc for the treatment of MDR-TB in children aged 6 years and older, in line with updated WHO treatment guidelines. The Committee noted that the extrapolation of evidence from adult data to children suggested therapeutic bedaquiline exposure in children and no increased safety risk.

Background

The application requested the addition of bedaquiline to the complementary list of the EMLc as a reserve second-line medicine for the treatment of multidrug resistant tuberculosis (MDR-TB) in children aged 6 years and older. In 2015, bedaquiline was included on the complementary list of the EML as a reserve second-line medicine for treatment of MDR-TB in adults (1).

Public health relevance

It is estimated that of the 10 million people who developed TB in 2017, 1 million of them were children. Children aged < 15 years accounted for 7.1% of the 6.4 million new or relapsed cases of TB notified to national TB programmes and reported to WHO. Children aged < 15 years accounted for 15% and 10% of total TB deaths among HIV-negative and HIV-positive people, respectively – higher than their share of estimated cases, suggesting poorer access to diagnosis and treatment. In 2017, it was estimated that about 558,000 new MDR-TB/ RR-TB cases emerged and about 230,000 MDR-TB/RR-TB patients died (2). The contribution of bedaquiline to MDR-TB regimens is crucial to compose regimens, particularly in frequent situations in which other effective and safe medicines are not available. In a substantial proportion of MDR-TB/RR-TB patients the susceptibility to fluoroquinolones is lost and other TB medicines cannot be given because of safety concerns. Reports of sporadic cases and outbreaks of MDR-TB and

XDR-TB among patients not previously treated for TB attests to the transmissibility of such strains, an additional public health concern, making the provision of effective treatment for all M/XDR-TB patients very important. The likelihood of treatment success in MDR-TB patients diminishes with the acquisition of additional drug resistance. Bedaquiline can increase the prospects of lasting cure in these patients. The WHO Global TB Programme considers that bedaquiline should also be viewed as an essential medicine in children aged 6 years and older following the update by WHO of its treatment recommendations for adults and children with MDR-TB/RR-TB in December 2018 (3).

Benefits

As part of the WHO guideline development process, a meta-analysis of individual patient data with 13 104 records from 53 studies in 40 countries was used to evaluate treatment success of bedaquiline. This dataset was largely composed of adult patients, with only 181 of the 13 104 (1.4%) cases being under 15 years of age. Paediatric data for bedaquiline were reviewed to explore the extent to which adult data could be extrapolated to children. The focus of this review was on safety and pharmacologic exposure data available from two ongoing paediatric studies of bedaquiline: TMC207-C211 and IMPAACT P1108 (4). Assuming that bedaquiline exposure-response (efficacy) profiles could be extrapolated from adults to children, the WHO Guideline Development Group concluded that the bedaquiline doses evaluated in the trials did not appear to produce bedaquiline exposures that would put children aged 6 to 17 years at greater risk of therapeutic failure.

Harms

With regard to harms, the Guideline Development Group concluded that the safety risk of bedaquiline in children aged 6 years and older did not appear to exceed that observed in adults. However, it was noted that children included in the trials were all HIV negative and had limited exposure to other QT-interval prolonging medicines (4).

Cost / cost effectiveness

Bedaquiline is available via the Global Drug Facility (GDF), at a price of US\$ 400 for a 6-month course of adult treatment (5). There is a marked differential in the price of bedaquiline between HICs and countries eligible for concessional pricing through the GDF. Prices for a 6-month course of adult treatment have been reported as EUR 26 481 in Italy (6), £ 18 880 in the United Kingdom (7) and US\$ 26 500 in the Republic of Korea (8).

WHO guidelines

The 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment (3) make the following recommendation with regard to bedaquiline: “Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more (strong recommendation, moderate certainty in the estimates of effect). Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years (conditional recommendation, very low certainty in the estimates of effect).” The updated guidelines include a weight-based dosage regimen for children 6–17 years: 15–29 kg: 2 x 100 mg tablets once daily for two weeks, then 1 x 100 mg tablet once daily on Monday, Wednesday and Friday for 22 weeks; >29 kg: 4 x 100 mg tablets once daily for 2 weeks then 1 x 100 mg tablets once daily on Monday, Wednesday and Friday for 22 weeks (equivalent to the adult dose).

Availability

Bedaquiline is manufactured by Janssen Pharmaceuticals. It is available to eligible countries through the GDF.

Other considerations

The Committee recalled that bedaquiline is associated with an increased risk of QT interval prolongation, which may be further increased when bedaquiline is administered with other medicines that prolong the QT interval. The Committee also noted the potential for drug–drug interactions between bedaquiline and other commonly co-prescribed medicines. These factors should be taken into consideration when bedaquiline is prescribed.

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5. Stop TB Partnership - Global Drug Facility (GDF) - GDF Products List [website]. (<http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp>, accessed 22 February 2019).
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