





		EMLc	ATC codes: J04AK06		
Indication	Multi-drug resistant Mycobacterium tuberculosis	ICD11 code: ML32.00			
INN	Delamanid				
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 > dispersible tablet: 25 mg (EMLc) Oral > Solid > tablet: 50 mg				
EML status history	First added in 2015 (TRS 994) Changed in 2017 (TRS 1006) 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	Delamanid 				
DrugBank	Delamanid 				

Expert Committee recommendation

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

Background

Delamanid 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 phase I, open-label, age de-escalation study, followed by a phase II 6-month extension study assessed the pharmacokinetics, safety and tolerability of delamanid administered twice daily for 10 days in children with MDR-TB/RR-TB aged birth to 17 years on treatment with an optimized background regimen (4). Twelve children were included in the 0–2-year cohort. Exposures in this age group were lower than predicted from pharmacokinetic modelling of older age groups, and lower than target exposures in adults, necessitating a modelling/simulation approach to dosing. A descriptive analysis of data from a paediatric MDR-TB/RR-TB individual patient dataset included seven children younger than 3 years treated with delamanid, 14 children aged 3–6 years and 69 children aged 6–12 years. All 21 children younger than 6 years were successfully treated (5). These data were reviewed by the Guideline Development Group responsible for updating the WHO guidelines on the management of tuberculosis in children and adolescents, which made a conditional recommendation based on very low certainty of evidence that delamanid may be used as part of longer regimens in children younger than 3 years with - or rifampicin-resistant tuberculosis (5–7).

Harms

From the evidence described above, no cardiac safety signals distinct from those reported in adults were observed in children 0–2 years of age. However, children had lower drug exposures compared with adults. Pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children younger than 3 years, even if higher doses were used to reach drug exposures comparable to those achieved in adults. Central nervous system effects, including paraesthesia, tremors, anxiety, depression and insomnia, are potential safety concerns associated with delamanid in both adults and children. Hallucinations have been associated with delamanid and are reported to be more prevalent in children than in adults (7). Overall, the Guideline Development Group considered the balance between desirable and undesirable effects of delamanid in children younger than 3 years probably favoured the intervention (7).

Cost / cost effectiveness

Information on the cost and cost-effectiveness of delamanid 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 delamanid may be used as part of longer regimens in children younger than 3 years with MDR-TB and RR-TB (5).

Availability

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

Other considerations

In October 2021, WHO convened an expert consultation on delamanid dosing in young children. During this consultation, it was noted that since safety concerns about a possible risk of metabolite accumulation largely applied to infants (younger than 3 months) with immature cytochrome P450 enzyme function, it was advised that dosing for infants weighing 5 kg to less than 10 kg should use a combined age- and weight-based approach, with doses for children younger than 3 months being lower than doses for children aged 3 months and older. Dosing guidance for delamanid in children is provided in the WHO operational handbook on tuberculosis (8). Use of the 25 mg dispersible tablet formulation is preferred in infants and young children, rather than manipulation of the 50 mg tablet.

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. García-Prats AJ, Frias M, van der Laan L, De Leon A, Gler MT, Schaaf HS, et al. Delamanid added to an optimized background regimen

en in children with multidrug-resistant tuberculosis: results of a phase I/II clinical trial. *Antimicrob Agents Chemother*. 2022;66(5):e0214421.

5. 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).

6. 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).

7. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. Web Annex 3: GRADE evidence to decision tables. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/352509>, 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).

