Application for the removal of the age cutoff for delamanid from the WHO Model Lists of Essential Medicines

WHO Global Tuberculosis Programme

1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

This application concerns the updating of the forthcoming WHO Model Lists of Essential Medicines (EML and EMLc) to propose to remove the age limit for the use of delamanid, (currently listed in the EML and EMLc for use in children aged 3 years and above) in line with updated WHO guidelines.

Delamanid has featured as an antituberculosis medicine on the complementary list of section *6.2.5 Antituberculosis medicines* since 2015 (WHO EML) and 2017 (WHO EMLc). In 2021, a child-friendly formulation of delamanid (25 mg dispersible tablet) was included in both the WHO EML and EMLc. In May-June 2021, a guideline development group (GDG) reviewed pharmacokinetic and safety data on the use of delamanid in children aged below 3 years. In March 2022, WHO released updated guidelines on the management of TB in children and adolescents, including a new recommendation on the use of delamanid in children with MDR/RR-TB as part of longer (individualized) treatment regimens aged below 3 years.[1] At the same time, WHO also published an operational handbook which provides dosing guidance on delamanid to ensure that this new recommendation could be implemented using the available formulations.[2]

Delamanid can therefore be used in children of all ages to treat MDR/RR-TB as a group C drug in individualized longer regimens. This new recommendation, alongside the new recommendation to expand the age indication for bedaquiline, makes it possible to build all-oral treatment regimens for all children with MDR/RR-TB.

The implementation of this new recommendation is enabled by the availability of a 25 mg dispersible tablet formulation of delamanid, as well as a 50 mg tablet formulation which can be administered whole or after being crushed and dispersed in water, without affecting its bioavailability.[3] Both formulations are already listed in the EML and EMLc.

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

This application is made by the WHO Global Tuberculosis Programme (GTB), Geneva, Switzerland and the focal points are: Tiziana Masini, Sabine Verkuijl, Annemieke Brands and Kerri Viney (WHO/HQ/UCN/GTB/VCC)

3. OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

The Sentinel Project on Drug-Resistant Tuberculosis and the TB Procurement and Market-Shaping Action Team (TPMAT) were consulted and are supporting the application.

4. KEY INFORMATION FOR THE PROPOSED MEDICINES

Delamanid is already listed in the WHO EML and EMLc. This information has been provided in previous applications and it is summarized below:

INN	ATC code	Dosage forms & strengths	ICD-11 code
delamanid	J04AK06	Tablet (dispersible): 25 mg Tablet: 50 mg	XM1FD5

5. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS/THERAPEUTIC GROUP

Delamanid is already listed in the WHO EML and EMLc as an individual medicine. This application is being made to expand the age group in which delamanid can be used, aligned to the latest WHO recommendations.

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

The detection and treatment of TB and drug-resistant TB in children and adolescents is a global public health priority. The estimated incidence of TB disease in children less than 15 years of age was 1.15 million in 2021.[4] Globally, the number of TB notifications among children and young adolescents aged 0-14 years old increased from less than 400,000 in 2015 to 523,000 in 2019, but a 24% drop was observed in 2020 due to the Covid-19 pandemic. As of 2021, a 15% drop is still observed in TB notifications among children and young adolescents aged 0-14 years old, compared to 2019. It is estimated that 209,000 children 0-14 years died of TB in 2021, with 80% of these deaths in children aged less than 5 years.

Children treated for TB have good treatment outcomes (88% treatment success rate was noted in the 2020 patient cohort for those with drug-susceptible TB) but, without treatment, mortality from TB is as high as 43% among children less than 5 years of age.[4]

MDR-TB is also a major global public health problem with an estimated 450,000 cases in 2021. While the exact burden of MDR-TB in children remains unknown, more than 30,000 cases of MDR-TB in children are estimated globally each year.[5,6] Since 2020, countries have reported on the number of children and young adolescents (0-14 years) initiated on second-line treatment for MDR/RR-TB. In 2021, 5506 children and adolescents <15 years were reported to be initiated on second-line treatment for MDR/RR-TB in 74 countries.

In September 2018 at the United Nations High Level Meeting (UNHLM) on the fight against TB, Heads of State agreed on the following global TB treatment targets aligned to the Sustainable Development Goals and the WHO End TB Strategy: 40 million people with TB to be reached with care during the period 2018 and 2023, including 3.5 million children and 1.5 million people with DR-TB (including 115,000 children with DR-TB). However, data in the latest Global TB Report 2022 show that we are far from reaching these targets, especially for children with TB. The total number of children treated for MDR/RR-TB in the period 2018–2021 is 17,726, which corresponds to only 15.4% of the 5-year target of 115 000. With only one year left to the 2023 UNHLM on TB, it seems unattainable to achieve this target.

Delamanid is expanding the list of medicines available for the design of individualized regimens, it has a favourable safety profile and can play a role in moving away from the use of injectable agents for the treatment of MDR/RR-TB particularly in children with already restricted options due to a more extensive resistance profile. Injectable agents carried the risk of permanent hearing loss, having a profound impact on language acquisition, ability to learn at school and further development.

7. TREATMENT DETAILS

Delamanid dosage regimen and duration of treatment (children and adolescents below 46 kg)

Acknowledging the importance of providing dosing guidance to ensure the new WHO recommendation on the use of delamanid in children of all ages can be implemented at country level, WHO convened an expert consultation on dosing related to this new recommendation in October 2021.[7] The meeting participants reviewed available PK, pharmacodynamic (PD) and safety data from recently completed trials (Otsuka 232 and 233 trials), and data from dosing simulations that were undertaken using the paediatric population PK model developed for the Otsuka 232 and 233 trials.

The doses used in the Otsuka 232 and 233 trials could not be directly used for WHO recommendations because the dosing strategy was age-based in the trials, whereas WHO recommends weight-based dosing. Also, the dosing used in the Otsuka 232 and 233 trials for the youngest children (aged 0–2 years) resulted in low delamanid exposures.

During the WHO convened consultations it was noted that since safety concerns largely applied to infants (aged below 3 months) with immature cytochrome P450 enzyme function (with the concerns relating to a possible risk of metabolite accumulation), 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 aged below 3 months being lower than doses for children aged 3 months and above. For children weighing 16 kg to less than 30 kg, the meeting participants advised using a 50 mg morning dose and a 25 mg evening dose, to balance practical administration of required doses with target exposures and to align dosing with guidance from the European Medicines Agency.

Participants noted that, based on their clinical experience, delamanid is generally well tolerated, and the safety profile is acceptable given the context in which the drug is used. Neuropsychiatric adverse events (including hypnopompic hallucinations) have been noted but are usually resolved when other drugs with similar effects are stopped. Participants judged that the consequences of underdosing far outweigh the consequences of overdosing in the context of MDR/RR-TB treatment, especially considering that delamanid is likely to be used in case of additional resistance to, drug intolerance to or unavailability of the Group A or B medicines when using longer regimens. Therefore, the resistance profile may be extensive when delamanid is used.

Figure 1 shows the dosing strategy developed, which was included in the *WHO operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents (Annex 6).*[8] Dosing guidance on delamanid may be updated as new evidence emerges.

In children weighing below 46 kg, dosing guidance is provided using the 25 mg dispersible tablet formulation (which has been shown to have good acceptability and palatability) and with the 50 mg adult tablet. The two formulations have essentially the same bioavailability.[9] The dosing guidance clearly indicates that the use of child-friendly, dispersible tablets in infants and young children is preferred over manipulating adult tablets. However, delamanid adult tablets (50 mg) crushed and suspended in water have been shown to have similar bioavailability as whole tablets and can be used to treat MDR/RR-TB in children if the dispersible tablet formulation of delamanid is unavailable or to facilitate administration in children who cannot swallow whole tablets.[3] It is possible to prepare sugar-containing and sugar-free extemporaneous liquid formulations of

delamanid using the adult 50 mg tablet. Preliminary results have shown that this formulation is chemically and microbiologically stable over 15 days (or more), depending on the preparation (*Benefit Kids project, unpublished data*).[10]

For dosing of delamanid in premature and low birth weight infants weighing <3 kg and ideally for infants weighing 3 to < 5 kg as well, advice from a paediatric DR-TB expert should be sought.

Figure 1. Dose of delamanid in people below 46 kg (*Module 5: Management of tuberculosis in children and adolescents (Annex 6)*

Group	Medicine	Weight-based daily dose[b]	Formulations (mg/mL, as applicable)	Weight bands[a]							Usual upper daily dose[b]	Comments
				3 to <5 kg	5 to <7 kg	7 to <10 kg	10 to <16 kg	16 to <24 kg	24 to <30 kg	30 to <36 kg	36 to <46 kg	
C	Delamanid	-	25 mg dt[j]	1 od	<3 months: 1 od ≥ 3 months: 1 bd		1 bd	2 morning 1 evening		2 bd	2bd	-
			50 mg tab[j] (50 mg in 10 mL = 5 mg/mL)	5 mL (0.5 tab) od[c]	<3 months: 5 mL (0.5 tab) od[c] ≥ 3 months: 5 mL (0.5 tab) bd[c]		5 mL (0.5 tab) bd[c]	10 mL (1 tab) morning 5 mL (0.5 tab) evening		1 bd[k]	1 bd[k]	

The available evidence of delamanid use is currently limited to the on-label 6-month duration alongside other medicines in a longer regimen; prolongation beyond 6 months can be considered on a case-by-case basis.[11]

Requirements to ensure appropriate use of the medicine(s)

Delamanid should be administered with food, ideally with a high-fat meal. However, taking delamanid with any food should be considered sufficient and the lack of a high-fat meal should not be a barrier to taking delamanid. In neonates, there are higher feeding frequencies, which aligns well with the goal of administering delamanid with high-fat nutritional content.

For children, routine clinical and safety monitoring of MDR/RR-TB treatment should generally follow the recommended approach in adults and should be guided by the known adverse effect profile of the medicines included in the regimen. The most common adverse effects associated with delamanid include nausea and vomiting, dizziness, paraesthesia, anxiety, QTc prolongation, hallucinations and night terrors.

Monitoring the emergence of neuropsychiatric effects (including hallucinations) in children treated with delamanid – both who are admitted to hospitals and treated in households is important. Particular attention should be paid to children who are receiving other medications that have known neuropsychiatric effects, such as cycloserine. Therefore, active TB drug safety monitoring and management systems must be functional to detect, manage and report suspected or confirmed drug toxicities in a timely manner.

Patients receiving delamanid in combination with other potentially QT-prolonging medicines (e.g. clofazimine, bedaquiline or the fluoroquinolones, especially moxifloxacin) should have regular electrocardiogram (ECG) monitoring, ideally at baseline, 2 weeks and 4 weeks, and then every 4 weeks while on treatment and additionally, as clinically indicated. Given the composition of currently recommended regimens, most people being treated for MDR/RR-TB will be receiving

one or more QT-prolonging medicines and will need ECG monitoring. The risk of a severely elevated QT interval (QTcF ≥500 ms) does not appear to be high in children or adolescents.[12]

Management of QTcF prolongation in children should follow the same steps as in adults, with symptom assessment, repeat of the ECG, electrolyte assessment and electrolyte replacement if relevant, nutritional assessment, thyroid function testing (if on ethionamide or P-aminosalicylic acid), and review of other medicines and possible clinical conditions. A QTcF over 450 ms is considered prolonged.[13]

Given that a QTc evaluation prior to delamanid administration may not always be feasible, it may be important to adopt risk mitigation strategies when administering delamanid in combination with other agents that prolong QTc (such as monitoring electrolytes).

Monthly monitoring of body weight is especially important in children and adolescents, with adjustment of the dose for delamanid and other drugs as the child gains weight. In infants, depending on their age, more regular monitoring of body weight is advised.

The risk of emergence of delamanid resistance should be a key consideration when the drug is being used. Due to the difficulties in obtaining a suitable sample from children aged below 3 years, performing DST may be challenging. However, if there are concerns about acquired drug resistance, every effort should be made to obtain a suitable sample, such as through gastric aspirate, sputum induction or NPA.

Adherence counselling and support for the child or adolescent and their family is a crucial part of effective care for MDR/RR-TB.[14] Information on adherence counselling and support, as well as more information on clinical monitoring for children and adolescents treated with bedaquiline and other second-line TB drugs can be found in the *WHO Operational Handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents*.

Recommendations in existing WHO guidelines that are relevant for this application

- In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens *(conditional recommendation, very low certainty of evidence)*[1]

8. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

The guideline development group considerations on the desirable and undesirable effects, certainty of the evidence, values, balance of effects and other relevant considerations on the PICO question related to delamanid (*Should an all-oral regimen containing delamanid vs. other WHO regimens without delamanid be used for MDR/RR-TB patients aged below 3 years?*) that are part of the Evidence to Decision (EtD) tables are included in the guidelines published in March 2022 and are summarized below.[1, 15]

The guideline development group (GDG) meeting convened by WHO in May-June 2021 reviewed data from a phase I, open-label, age de-escalation trial designed to assess the PK, safety and tolerability of delamanid administered twice daily for 10 days in children with MDR/RR-TB on treatment with an optimized background regimen (protocol 242–12–232) and from the

corresponding open-label extension study (protocol 242–12–233). Data from cohorts 1 (age 12–17 years), 2 (age 6–11 years), 3 (age 3–5 years) and 4 (age 0–2 years) for both protocols were reviewed. Exposures in the 0–2 year age group were lower than those of children aged 3 years and older, necessitating a modelling/simulation approach to dosing.

In addition to data from the trials, data from a paediatric DR-TB IPD were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The paediatric DR-TB IPD included only seven children aged below 3 years treated with delamanid, 14 children aged 3–6 years, and 69 children aged 6–12 years. All 21 children aged below 6 years were successfully treated. The number of children was insufficient for a matched analysis.

The GDG noted that when the delamanid phase II trial was started, many of the companion drugs in the optimized background regimen were not widely available (such as linezolid and moxifloxacin). By the time the phase III trial started, linezolid and moxifloxacin became more accessible, which meant that the optimized background regimens in the trial were likely more effective, making it more difficult to prove the added effect of a drug (i.e. delamanid) in the intervention regimen. The GDG concluded that the desirable effects are small. However, it was noted that when looking at specific populations such as people with pre-XDR-TB, the desirable effects may be rated differently – e.g., in this case the desirable effects would be rated as moderate rather than small.

The GDG discussion around the undesirable effects focused on adverse events, including those related to the central nervous system and cardiac toxicities, as well as the newly reported adverse event of hallucinations which was of some concern to GDG members given the period of dynamic brain development in children (*see section 9 below*).

The GDG considered that the risks and benefits (and balance of both) are very different for treating a child with resistant forms of TB (i.e. MDR/RR-TB and XDR-TB) and with limited treatment options, compared to a healthy child at future risk of developing MDR-TB (i.e. where delamanid is used for prevention). Therefore, the GDG concluded that the balance between desirable and undesirable effects probably favours the intervention.

9. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY

The guideline development group considerations on the desirable and undesirable effects, certainty of the evidence, values, balance of effects and other relevant considerations on the PICO question related to delamanid (*In MDR/RR-TB patients aged below 3 years, should an all-oral treatment regimen containing delamanid versus other regimens conforming to WHO guidelines without delamanid be used?)* that are part of the Evidence to Decision (EtD) tables are included in the guidelines published in March 2022 and are summarized below.[**Error! Bookmark not defined.**, 16]

The GDG considerations on the desirable and undesirable effects, certainty of the evidence, values, balance of effects and other relevant considerations on the PICO question related to delamanid (*Should an all-oral regimen containing delamanid vs. other WHO regimens without delamanid be used for MDR/RR-TB patients aged below 3 years?*) that are part of the Evidence to

Decision (EtD) tables are included in the guidelines published in March 2022 and are summarized below.[1, 17]

No cardiac safety signals distinct from those reported in adults were observed in children 0–2 years of age. However, these findings should be considered knowing that children had lower drug exposures compared to adults. However, pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children under 3 years of age, even if higher doses were used to reach drug exposures comparable to those achieved in adults.

Central nervous system effects were included in the delamanid label for both adults and children (paraesthesia, tremors, anxiety, depression and insomnia) as important potential safety concerns for the drug. In March 2021, the study sponsor released a statement of intent to modify the labelling to include hallucinations as an adverse reaction. This new safety signal has been more prevalent among children (versus adults) with 15 reports in 14 children 2–16 years of age in India, Philippines, South Africa, Tajikistan and Ukraine. Children experiencing this safety signal included some with extensively resistant forms of TB (MDR/XDR-TB) treated with delamanid under programmatic conditions (12 reports) as well as children enrolled in a clinical trial studying delamanid for TB prevention (three reports). Seven of the 15 reports were for children also receiving cycloserine (under programmatic conditions). The GDG noted the importance of side-effects involving the central nervous system in young children, considering their dynamic brain development.

As mentioned above, The GDG considered that the risks and benefits (and balance of both) are very different for treating a child with resistant forms of TB (i.e. MDR/RR-TB and XDR-TB) and with limited treatment options, compared to a healthy child at future risk of developing MDR-TB (i.e. where delamanid is used for prevention). Therefore, the GDG concluded that the balance between desirable and undesirable effects probably favours the intervention.

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

Information on the cost and cost-effectiveness of delamanid has been provided in previous applications. There is no additional updated information in this regard.

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

Information on the regulatory status, market availability and pharmacopoieal standards has been provided in previous applications. There is no additional updated information in this regard.

References

[1] WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240046764 (accessed 22 November 2022).

[2] WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240046832 (accessed 22 November 2022).

[3] Zou Y, Svensson E, Hesseling AC, et al. Relative bioavailability of delamanid 25mg, 50mg and 100mg, administered to healthy adults under fed conditions dispersed in water compared to tablet form: a randomized crossover study. BENEFIT Kids Project, 2022, submitted to *British Journal of Clin Pharmacology*, under review.

[4] Global tuberculosis report 2022. Geneva: World Health Organization; 2022. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022 (accessed 22 November 2022).

[5] Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572–1579.

[6] Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. Lancet Infect Dis. 2016;16(10):1193–1201.

[7] Report of a WHO expert consultation on dosing to enable implementation of treatment recommendations in the WHO consolidated guidelines on the management of TB in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240055193 (accessed 22 November 2022).

[8] WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://www.who.int/publications/i/item/9789240046832 (accessed 22 November 2022).

[9] Sasaki T, Svensson EM, Wang X, Wang Y, Hafkin J, Karlsson MO et al. Population pharmacokinetic and concentration-QTc analysis of Delamanid in pediatric participants with multidrug-resistant tuberculosis. Antimicrob Agents Chemother. 2021;66(2):e01608–21.

[10] Nahata MC, Scarim J, Scarim A, et al. Stable sugar and sugar-free liquid formulations of delamanid for use in patients with rifampicin- resistant tuberculosis. BENEFIT Kids Project, *unpublished data.*

[11] WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/332397, accessed 2 December 2021

[12] WHO operational handbook on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/332398, accessed 2 December 2021).

[13] WHO operational handbook on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/332398, accessed 2 December 2021).

[14] A family-centered approach to the treatment and prevention of drug-resistant tuberculosis in children and adolescents: Counselling tools and approach. Khayelitsha: Medecins Sans Frontieres; 2021 (http://sentinelproject.org/wp-content/uploads/2021/12/Peds_Counseling_Outline_V3.pdf, accessed 12 March 2022).

[15] WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Web Annex 3. GRADE Evidence to Decision Tables. Available from: https://apps.who.int/iris/bitstream/handle/10665/352509/9789240046801-eng.pdf?sequence=1&isAllowed=y (accessed 22 November 2022).

[16] WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Web Annex 3. GRADE Evidence to Decision Tables. Available from: https://apps.who.int/iris/bitstream/handle/10665/352509/9789240046801-eng.pdf?sequence=1&isAllowed=y (accessed 22 November 2022).

[17] WHO consolidated guidelines on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Web Annex 3. GRADE Evidence to Decision Tables. Available from: https://apps.who.int/iris/bitstream/handle/10665/352509/9789240046801-eng.pdf?sequence=1&isAllowed=y (accessed 22 November 2022).