Essential Medicines List (EML) 2021

Application for the inclusion of delamanid 25 mg dispersible tablet in the Complementary List of the WHO Model List of Essential Medicines for Children

General items

1. **Summary statement of the proposal for inclusion, change or deletion**

This application concerns the updating of the forthcoming WHO Model List of Essential Medicines for Children (EMLc) to include a formulation of 25 mg dispersible tablet of delamanid. This application proposes the addition of delamanid 25 mg dispersible tablet to the complementary list of the WHO EMLc in section in section 6.2.5 Antituberculosis medicines. Should this application result in the addition of a 25 mg tablet formulation of delamanid to the complementary list of the WHO EMLc, we also request a change to the age restriction from ≥6 years to ≥3 years, in line with current WHO recommendations on the use of delamanid (1, 2).

This application is not proposing to add a new medicine to the WHO EMLc, but to include a different strength of an existing one. Delamanid has featured as an antituberculosis medicine on the complementary list of the WHO EML and EMLc since 2015 and 2017, respectively, as a 50 mg tablet formulation, which is available on the market. All-oral longer regimens, which can include delamanid are recommended by WHO for children with multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) aged 3 years and above (1, 2). The availability of a child-friendly formulation of delamanid (25 mg dispersible tablet) could enable appropriate dosing of children aged 11 years old and younger, improving the likelihood of adherence to treatment in a particularly vulnerable population.

This is particularly important:

- given that countries are transitioning from injectable-based regimens to all-oral regimens for the treatment of MDR/RR-TB, based on WHO recommendations.
- recognising the global push to have dispersible tablet formulations of paediatric TB medicines.
- given that delamanid is a recommended medicine for the treatment of MDR/RR-TB and only one of three new TB compounds that have been recommended in recent years.
- given current WHO dosing recommendations for the use of delamanid in children.
- recognising that some clinicians are splitting the 50 mg tablets to treat children, which is not a recommended practice, and
- given that the 50 mg tablets are proven not to be bioequivalent to the 25 mg formulation and considering that when the 50 mg tablet (unscored) is broken, the contents are bitter and unpalatable, and the impact of crushing could appreciably alter (most likely reduce) the bioavailability of delamanid.

2. Relevant WHO technical department and focal point

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

3. Name of organizations consulted and/or supporting the application

The Stop TB Partnership's (STBP) Global Drug Facility (GDF) was consulted and is supporting the application.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

The USAN INN (generic name) of the medicine concerned is delamanid (3). The Anatomical Therapeutic Chemical (ATC) code of the medicine concerned is J04AK06. [a]

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

[a] https://www.whocc.no/atc_ddd_index/?code=J04AK06; accessed 10 December 2020.

The proposed formulation is a Delamanid 25 mg dispersible tablet (child-friendly formulation). The product is currently available from the manufacturer (Otsuka) *via* Compassionate Use (4). Market availability of this product is foreseen in late 2021.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

The application is for the inclusion of Delamanid 25 mg dispersible tablet to the Complementary List of the WHO EMLc as an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring).

Delamanid is a nitro-dihydroimidazooxazole, currently classified by the WHO as a Group C drug for the treatment of MDR/RR-TB as part of longer regimens.[b] Group C drugs are to be used in a treatment regimen when medicines from Groups A and B cannot be used (1). Delamanid is one of only a few new TB medicines that have been approved by stringent regulatory authorities in the last few years and was first recommended for use by WHO in 2014, when they issued interim policy guidance on its use. The interim policy guidance stated that "delamanid may be added to an MDR-TB regimen in adult patients with pulmonary TB (5)." In 2016, the delamanid interim policy was extended to children aged 6-17 years, following a review of data from a 6-month safety, efficacy, and pharmacokinetic trial of paediatric patients (6). In January 2018, WHO issued a position statement on the use of delamanid in the treatment of MDR-TB (7). Based on a review of data from a phase III, multicentre, randomized, double-blind, placebo-controlled clinical trial, an expert review panel concluded that the prevailing interim and conditional guidance on delamanid should remain in place. Then, in 2018 additional paediatric data on the use of delamanid were reviewed to examine whether the recommendations for delamanid use in children could be further lowered to children under 6 years of age. The focus of this review was on safety and pharmacologic exposure data available from ongoing paediatric studies. At this time, the WHO convened Guideline Development Group (GDG) who reviewed these data recommended that delamanid could be safely used in children aged 3 years and above (8). (**Figure 1**)

Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients under 15 years old[a]							Usual upper daily dose[b]	Comments
			5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
Delamanid	–	50 mg tab	–	–[f]	–[f]	–[f]	1 bd	1 bd	2 bd	200 mg	Only in patients aged >2 years (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years).

f May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.

Figure 1. Dosing of Delamanid in multidrug-resistant TB regimens by weight band (patients under 15 years) (*source: WHO operational handbook on tuberculosis, module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. Available from: https://www.who.int/publications/i/item/9789240006997)*

However, at the time, the GDG also noted their concerns about the feasibility of administering the correct dose to children aged 3–5 years, given that the special formulation used in the trial (i.e., a 25 mg dispersible tablet formulation) would not be available in the foreseeable future. At that time, only the adult tablet was available (i.e., 50 mg tablet), and based on the data assessed, there were concerns that bioavailability may be altered if the 50 mg tablet was split, crushed or dissolved.[c] Delamanid 50 mg tablet is also susceptible to oxidation and

[b] These are defined as regimens that are used for treatment of multidrug- or rifampicin-resistant TB (MDR/RR-TB). These regimens last 18 months or more, and are designed using a hierarchy of recommended medicines, including a minimum number of medicines considered to be effective based on drug-resistance patterns or patient history.

[c] The delamanid adult formulation and pediatric formulation are not bioequivalent. In a crossover bioequivalence (BE) study, neither Cmax [90%CI GMR 0.701,0.809] nor AUC [90%CI GMR 0.775,0.909] satisfied the criteria for BE as specified by regulatory agencies. As such, the formulations are not interchangeable. Substituting the adult formulation for the pediatric formulation will result in higher delamanid exposures than would be expected from the pediatric formulation. **Error! Bookmark not defined.**

heat, and therefore retaining pill fragments for use at any time other than the time of administration will likely result in the delivery of lower-than-expected active compound and unspecified oxidation by-products. The content of broken 50 mg tablets was also noted to be bitter and unpalatable. (*see page 181-184 of: WHO consolidated guidelines on drug-resistant tuberculosis treatment. Annexes 8-10 (WHO/CDS/TB/2019.3). Geneva, World Health Organization. 2019. Available from: https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf*) (9).

Despite these limitations, clinicians and paediatric experts in the field have been manipulating the 50 mg delamanid formulation (either by splitting the tablet and then discarding the remaining part, or by administering the 50 mg tablet once a day, so no manipulation of the tablet is required), as this is the only option currently available to them when delamanid is used in young children (10). Delamanid is an essential medicine for young children with MDR/RR-TB and extensively-drug (XDR-)TB, a more severe form of DR-TB.[d] In many low resource settings, delamanid is often used to replace painful injectable agents that have several side effects when designing all-oral regimens for young children (11). As shown by the results from a recent survey of policies and practice on TB prevention, testing and treatment in 37 high TB burden countries, more and more countries are transitioning to injectable-free, all-oral regimens for children with uncomplicated drug-resistant TB. Among the countries surveyed, 72% had policies indicating the use of these regimens for children (11), with most of the regimens reported including delamanid (12). In light of these findings, it becomes more important to include child-friendly formulations in the WHO EMLc, so that countries can promptly access them.

It should also be noted that many countries are already using delamanid as part of short, all-oral regimens under operational research conditions (12).

8. Information supporting the public health relevance

The detection and treatment of TB and DR-TB in children and adolescents is a global public health priority. Child and adolescent TB is often overlooked by health providers and can be difficult to diagnose and treat.
It is estimated that 7.5 million children and young adolescents (0-14 years old) are infected with TB each year (13). The estimated incidence of TB in children less than 15 years of age (i.e., children who develop active TB disease) was 1.2 million in 2019. 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. It is estimated that 230,000 children 0-14 years died of TB in 2019 with 80% of these deaths happening in children aged less than 5 years. Children treated for TB have excellent outcomes (84% treatment success rate in the 2018 patient cohort) but, without treatment, mortality from TB is as high as 43% among children less than 5 years of age (14).
Even if the exact burden of MDR-TB in children remains unknown, more than 30,000 incident cases of multidrug-resistant TB (MDR-TB) in children are estimated globally each year. In 2020, for the first time, countries also reported on the number of children and young adolescents (0-14) initiated on second-line treatment for MDR/RR-TB (*see Table B5.3.1, source: Global TB Report 2020*)

TABLE B5.3.1

Numbers of people enrolled in treatment for MDR/RR-TB, for all ages and for children, 2018–2019

	ALL AGES	CHILDREN AGED 0–14 YEARS	SHARE OF CHILDREN IN TOTAL (%)
2018	156 205	3 398	2.2%
2019	177 099	5 586	3.2%

In September 2018, Heads of State agreed on the following major global targets: 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) (15). However, data in the latest Global TB Report 2020 show that we are far from reaching these targets, especially for children with TB (**Figure 2**). The total number of children treated for MDR/RR-TB in 2018–2019 is 8986, which corresponds to only 7.8% of the 5-year target of 115 000.

The Roadmap towards ending TB in children and adolescents, launched just prior to the UNGA High-Level Meeting (HLM) on TB, includes milestones towards reaching these targets, including access to shorter and safer

[d] The definition of XDR-TB is currently being updated by WHO, following a WHO Consultation held in October 2020.

child-friendly regimens for prevention and treatment of drug-susceptible and drug-resistant TB. Indeed, child-friendly formulations of TB drugs are essential to facilitate correct implementation of WHO recommendations for prevention and treatment of TB in younger children (16).

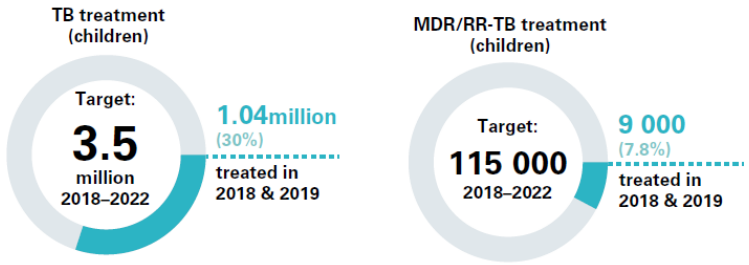

Figure 2. Global progress in the number of children treated for TB and MDR/RR-TB in 2018 and 2019 compared with cumulative targets set for 2018-2022 at the UN HLM on TB (*source: Global TB Report 2020*)

9. Review of benefits: summary of evidence of comparative effectiveness.

10. Review of harms and toxicity: summary of evidence of safety.

Delamanid was recommended for inclusion in the complementary list of the EML in 2015 for use in adults with MDR-TB, and for inclusion in the complementary list of the EMLc in 2017 for use in children aged 6 years and above with MDR-TB in 2017. The potential benefits and harms of delamanid have been extensively reviewed and summarised at the time of the original applications and the associated evidence is available in the technical reports of the meetings (17, 18).

Since the time of the original application in 2015, WHO assessed the relative effectiveness of second line medicines for MDR-TB during a GDG meeting. Based on data from Trial 213, delamanid was determined to have an adjusted odds ratio of 1.1 (0.4–2.8) when assessing the outcomes of treatment failure and relapse versus treatment success and 1.2 (0.5–3.0) when assessing death versus treatment success (1).

Based on the pharmacological and safety data reviewed by the GDG in 2018, including cohorts of patients 3-5 years old treated with Delamanid 25 mg dispersible tablet in Trials 232 and 233 (8), it was concluded that exposure profiles in children dosed with this formulation were comparable to adults and no safety signals distinct from those reported in adults were observed in this age group. (*see page 181-184 of: WHO consolidated guidelines on drug-resistant tuberculosis treatment. Annexes 8-10 (WHO/CDS/TB/2019.3). Geneva, World Health Organization. 2019. Available from: https://www.who.int/tb/areas-of-work/drug-resistant-tb/Annexes_8-10.pdf*) (9).

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

No data beyond the ones used in the original 2014 guidance are available.

Starting from April 2019, Delamanid 25 mg dispersible tablets were made available for compassionate use and can be obtained from Otsuka at no charge on a patient-by-patient basis (4). Otsuka has committed to making Delamanid 25 mg dispersible tablet available to the STBP's GDF at the lowest global price, per GDF's requirements (19).

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

In September 2020, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion for the use of delamanid to treat pulmonary multidrug-resistant TB in adolescents and children weighing at least 30 kg (20). Otsuka is expecting an EMA CHMP opinion for children weighing less than 30 kg in the coming months, and approval of the Delamanid 25 mg dispersible tablet formulation in late 2021 (19).

Delamanid 25 mg dispersible tablets are also included in the 23rd Invitation to Manufacturers to submit an Expression of Interest for Product Evaluation by the Global Fund Expert Review Panel (21). Otsuka is exploring potential submission to the Global Fund ERP in 2021 (19).

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

No reference standards for delamanid were found.

Standard	Status (accessed 16.11.2020)
British Pharmacopoeia	Not found
International Pharmacopoeia	Not found
United States Pharmacopoeia	Not found
European Pharmacopoeia	Not found

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