F.4	**Medicine: Delamanid 25 mg** **Indication: Multi-drug resistant tuberculous Mycobacterium**
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The roadmap towards ending TB in children and adolescents includes access to shorter and safer 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. In the context of global transition from injectable-based regimens to all-oral regimens for the treatment of adult and paediatric MDR/RR-TB, the availability of child-friendly formulations of Delamanid is advisable.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Delamanid is a recently approved drug for the treatment of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. According to the latest "WHO consolidated guidelines on Tuberculosis (2020)" Delamanid is classified as a "Group C drug" and is indicated as part of all-oral long term regimen for patients with multidrug and rifampicin-resistant tuberculosis (MDR/RR-TB). Delamanid, as oral 50 mg tablet formulation, has been included in the complementary list of the WHO-EML since 2015 and of WHO-EMLc since 2017 for children aged 6-18. The benefits and harms of the drug have been extensively reviewed in these 2 original applications. In 2019 paediatric data for Delamanid were reviewed by WHO-EMLc to examine whether the recommendations for Delamanid could be lowered to children under 6 years of age. According to WHO/GDG Delamanid was considered safe in children aged 3 years and above. However, the Expert Committee did not recommend the requested change to the age restriction, because the only source of delamanid at the time was the 50 mg adult formulation, which posed potential problems in terms of bioequivalence when considered for children under 6 years of age. Starting from April 2019, Delamanid 25 mg dispersable tablet formulation is available for compassionate use. This application review concerns • the request of inclusion of a "child-friendly formulation" of Delamanid (25 mg dispersable tablet) in the WHO EMLc • the change of age restriction from ≥6 years to ≥3 years.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? From the application: "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. (*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.*
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: From the application: "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.)*
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: From the Report of the WHO expert committee, 2017: "Fewer serious adverse events were reported in the RCT, with no evidence of higher rates of adverse events in delamanid-treated patients (RR 1.23; 95% CI 0.61–2.33). Exposure to delamanid was associated with a statistically significant increase in QT prolongation in adults and it was considered that this effect could be generalized to under- 18-year-olds (QT prolongation over 2 months, RCT, 9.9% vs 8.8%; RR 2.65; 95% CI 1.08– 5.99). QT prolongation by more than 60 ms was reported in 7.5% of delamanid-treated patients compared with no patients receiving an optimized background regimen (odds ratio (OR) 12.81; 95% CI 1.65–99.7). Acquired resistance to delamanid was not estimable in either the RCT or the open observational trial"

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Overall favourable benefit/risk ratio
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Moderate
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Active drug safety monitoring is required, particularly for QTc interval prolongation and cardiac dysrhythmias, as is monitoring of electrolyte disturbances (especially potassium)
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: • Deltyba (Delamanid 50 mg) was approved by European Medicine Agency (EMA) in 2020: "Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents and children with a body weight of at least 30 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability" • Delamanid 25 mg is under evaluation by EMA
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: From the "WHO consolidated guidelines on tuberculosis, 2020; Drug resistance tuberculosis treatment" • **Recommendation 3.8:** Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty in the estimates of effect)*
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Given that delamanid is a recommended drug by WHO latest guidelines for the treatment of MDR/RR-TB in children above 3 years, and 50 mg tablets are proven no to be bioequivalent 25 mg formulation, the availability of child-friendly formulation of the drug is needed.

Any additional comments	N/A
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	The Expert Committee to recommend the addition of Delamanid 25 mg dispersable tablet to the complementary list of WHO-EMLc for the treatment of children aged 3 years and above with multidrug and rifampicin-resistant tuberculosis (MDR/RR-TB), in line with the updated WHO treatment guidelines.
References (if required)	