F.4	Bedaquiline 20 mg tablets
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:
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.	Treatment of MDR-TB is substantially more complex, more toxic and less effective than standard therapy. The need for new therapeutic options is critical to reduce MDR-TB morbidity and mortality. Bedaquiline may represent an additional therapeutic option for treatment MDR-TB. The availability of the anti-MDR-TB drugs for children is therefore essential to successfully reduce the disease burden in children This application is to include bedaquiline 20 mg oral tablet on the complementary list of anti MDR-TB drugs in the EML and EMLc and to extend the current age recommendation (children ≥ 6 years) to children ≥ 5 years old and weighing at least 15kg for the bedaquiline 100 mg oral tablet in the EMLc.
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). There is no enough pharmacokinetic and bioequivalence studies including the 20 mg and trials in children. There is no palatability studies Since May 2020, bedaquiline is approved in the United States of America for the use in children 5 years and older and weighing above 15 kg. The available bedaquiline 20 mg tablet in conjunction with the WHO classification of bedaquiline as a priority drug for adults and children for the treatment of MDR-TB, is expected to play a crucial role in the treatment of MDR-TB in the younger children. The paediatric data are generated in the TMC207-C211 (NCT02354014), which is an ongoing, open-label, Phase 2 trial designed to evaluate the PK, safety, tolerability, and antimycobacterial activity of bedaquiline in combination with a BR of MDR-TB medications in children and adolescents. Fifteen MDR-TB paediatric patients (body weight at baseline: 14 to 36 kg) received bedaquiline (200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks) using the bedaquiline 20 mg tablet formulation in combination with a BR. Of these 15 paediatric patients, complete pharmacokinetic data were obtained for 10 patients at the aforementioned dosage regimen of bedaquiline. In 9 of these 10 paediatric patients who weighed at least 15 kg at baseline, the mean

	bedaquiline Cmax and AUC24h were similar to that of adult MDR-TB patients receiving the recommended adult dosage regimen. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☒ No ☐ Not applicable Comments: Further studies are required to recommend the use of bedaquiline in some populations such as children, HIV-infected persons, pregnant women, persons with extrapulmonary TB, and persons with co-morbid conditions. However, it can be used with caution in these populations if there are no other options available.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Bedaquiline may require special monitoring of cardiac and hepatic adverse events. Indeed, bedaquiline can affect the heart's electrical activity (QT interval prolongation), which could lead to potential severe cardiac toxicity (fatal heart rhythm). Patients should be monitored for symptoms of cardiac toxicity and by electrocardiogram (ECG). In addition, hepatic-related adverse drug reactions have been reported with the use of bedaquiline. Liver function (AST, ALT, bilirubin and alkaline phosphatase) should be tested at baseline, monthly, and if symptomatic.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Due to the potential for serious adverse events, this drug will not be recommended for all MDR-TB patients. The benefits of using bedaquiline for the treatment of MDR-TB may outweighed these harms in some populations especially the patients with additional resistance or contraindication to fluoroquinolones or to second-line injectable drugs.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Evidence of treatment outcomes is low to 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: Liver function tests are available in all laboratories as well as the availability of EGC for cardiac monitoring.

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:
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:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	There is a lack of drugs for the treatment of MDR-TB. This drug is not currently available in all countries. Its availability may provide an additional option for treatment and will improve clinical outcomes in pulmonary MDR-TB.
Any additional comments	
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.	Favorable for the introduction of this new strength. In another hand and due to the lack of data, the benefits of using bedaquiline for the treatment of MDR-TB in children should outweighed these harms in some populations especially the patients with additional resistance or contraindication to fluoroquinolones or to second-line injectable drugs.
References (if required)	