

F.5	Bedaquiline 20 mg - Multi-drug resistant tuberculous Mycobacterium
Does the application adequately address the issue of the public health need for the medicine?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: The spread of drug-resistant strains of M. tuberculosis is increasingly recognized as a major problem for children in countries with significant transmission of drug-resistant disease. The availability of the anti-MDR-TB drugs for children is therefore essential to successfully reduce the disease burden in children.
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.	According to the latest “WHO consolidated guidelines on Tuberculosis (2020)” Bedaquiline is classified as a “Group A drug”, and is recommended as a key anti-mycobacterial agent of both short-course and longer treatment regimens for MDR-TB in adults and children. In 2015, bedaquiline, as oral 100 mg tablet formulation, was included on the complementary list of the EML as a reserve second-line medicine for treatment of MDR-TB in adults and in 2019 was added to the complementary list of the EMLc as a reserve second-line medicine for the treatment of multidrug resistant tuberculosis (MDR-TB) in children aged 6 years and older. This application review concerns <ul style="list-style-type: none"> • The request of inclusion of an age appropriate and child-friendly formulation of bedaquiline (20 mg dispersible tablet) in the WHO EMLc • The request of modification of age restriction for Bedaquiline 100 mg from the current ≥ 6 years to ≥ 5 years and weighing ≥ 15 kg.
Have all important studies and all relevant evidence been included in the application?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> 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)? The benefits of Bedaquiline (100 mg) for children ≥ 6 years have been already extensively reviewed in 2019 by the expert committee which, assuming that bedaquiline exposure-response (efficacy) profiles could be extrapolated from adults to children, concluded that the bedaquiline doses evaluated in the trials did not appear to produce bedaquiline exposures that would put children aged 6 to 17 years at greater risk of therapeutic failure.

	<p>The 20 mg tablet formulation was evaluated in the ongoing paediatric trial TMC207-C211 (NCT02354014) in children ≥ 5 - <12 years of age. The C211 is an 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 0 months to <18 years of age who have confirmed or probable pulmonary MDR-TB.</p> <p>In 2020 interim data of trial of C211 were published. (Bedaquiline for multi drug-resistant, including extensively or pre-extensively drug-resistant, pulmonary mycobacterium tuberculosis in children." American Journal of Respiratory and Critical Care Medicine, 2020). The Week 24 primary analyses of Cohort 1 (≥ 12 to <18 years, using bedaquiline 100 mg tablets) and Cohort 2 (≥ 5 to <12 years, using bedaquiline 20 mg tablets), showed that Bedaquiline 20 mg was generally well tolerated and had a safety profile that is comparable to the safety profile of bedaquiline per recommended dose in adults and adolescents who received the 100 mg table.</p> <p>Of note, 15 patients ages 5 years to 10 years of age were enrolled in the second cohort. The median age was 7 years, 60% were female, 60% were Black, 33% were White and 7% were Asian. The body weight ranged from 14 kg to 36 kg; only one patient weighing 14 kg was enrolled. Bedaquiline was administered as 200 mg once daily for the first 2 weeks and 100 mg 3 times/week for the following 22 weeks using the 20 mg tablet in combination with an individualized MDR- TB treatment option. In the subset of patients with culture positive pulmonary MDR-TB at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 100% (3/3 patients) at Week 24.</p>
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>From the application</p> <p>Concerning the safety profile of Bedaquiline 20 mg, the week 24 analysis of C211 trial showed that among these 15 paediatric patients, no deaths occurred. The most common adverse reactions were related to increased transaminases including AEs of hepatotoxicity (3/15, 33%), that led to discontinuation of bedaquiline in three patients. Elevations in liver enzymes were reversible upon discontinuation of bedaquiline and some of the BR drugs. The selected bedaquiline dosing regimen for 24 weeks as part of MDR-TB therapy was generally safe and anticipated toxicities, were manageable with careful monitoring and modifications of the TB treatment regimen.</p>
Are there any adverse effects of concern, or that may require special monitoring?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>As previously recalled by the Expert committee review in 2019, bedaquiline is associated with an increased risk of QT interval prolongation, which may be further increased when bedaquiline is administered with other medicines that prolong the QT interval. This aspect should be taken into consideration when bedaquiline is prescribed.</p>
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	In line with the WHO guidelines for drug-resistant tuberculosis treatment, the benefit to risk ratio of bedaquiline in patients aged > 6 years with MDR-TB is favourable

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Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Only few data available from pediatric clinical trials. Very low certainty in the estimates of effect in children .
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)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments:
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)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: <ul style="list-style-type: none"> • Bedaquiline 20 mg tablet is approved by US FDA as part of combination therapy of pulmonary TB due to MDR-TB in children 5 to less than 18 years of age, weighing at least 15 kg. • Bedaquiline 20 mg is under evaluation by the European Medicines Agency
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)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: <p>WHO consolidated guidelines on tuberculosis. Drug-resistant tuberculosis treatment</p> <p>Recommendation 3.4</p> <p>Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. ^[1] (Strong recommendation, moderate certainty in the estimates of effect)</p> <p>Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. (Conditional recommendation, very low certainty in the estimates of effect).</p> <p>Recommendation 2.1</p> <p>A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. (Conditional recommendation, very low certainty in the evidence)</p>

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<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>From the application:</p> <p>A tiered pricing strategy for sustainable and affordable access to bedaquiline is being implemented globally. This comprehensive Access & Affordability approach is in view of the unique public health considerations of MDR-TB. It is Janssen's policy to communicate prices after regulatory approval and discussions with local health authorities.</p> <p>Bedaquiline 20 mg is accessible through GDF for 25,53 USD for a bottle of 60 tablets. This amounts to a price of 200 USD for a full treatment cycle (470 tablets/24 weeks) in children weighing 15 kg to less than 30 kg administering half the adult dose. Bedaquiline, 20 mg tablet is also indicated for adults and/or adolescents who have trouble swallowing, for which a complete treatment cycle would require 940 tablets (33).</p> <p>Janssen Pharmaceutica, N.V. has a long-term agreement with the International Dispensary Association (IDA) for the supply of bedaquiline by order and account of the Stop TB Global Drug Facility (GDF), which is an initiative that provides a unique package of services, including technical assistance in TB drug management and monitoring of TB drug use to patients in need in over 135 countries. To improve lead time for deliveries to countries GDF has setup a Strategic Rotating Stockpile (SRS), with unassigned stock always available at IDA.</p>
<p>Any additional comments</p>	<p>/</p>
<p>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.</p>	<p>The Expert Committee to recommend the addition of Bedaquiline 20 mg tablet formulation to the complementary list of WHO-EML and EMLc for the treatment of MDR-TB in adults and in children ≥ 5 years of age, in line with the updated WHO treatment guidelines.</p>
<p>References (if required)</p>	