M E M O R A N D U M

From:	Director, GTB	**To:**	Director, HPS	**Date:**	17 May 2021
Our ref:		**Attention:**	Secretary of the Expert Committee on Selection and Use of Essential Medicines		
Your ref:		**Through:**			
Originator:	MZ/FM/SV/tm/nb	**Subject:**	**COMMENTS TO APPLICATIONS FOR UPDATING OF SECTION 6.2.4 (ANTITUBERCULOSIS MEDICINES) IN THE MODEL LIST OF ESSENTIAL MEDICINES AND THE MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN**		

As requested in your memorandum, dated 11 March 2021 (WHOHQ-E19-81-17), the World Health Organization (WHO) Global TB Programme (GTB) has reviewed the following applications for the updating of the section 6.2.4 Antituberculosis medicines in the Model List of Essential Medicines (EML) and the Model List of Essential Medicines for Children (EMLc)

- Bedaquiline – addition of 20 mg tablet formulation to the EML and EMLc
- Pyrazinamide – addition of 500 mg oral formulation to the EML
- Ethambutol – addition of IV formulation to the EML
- Isoniazid – addition of IV formulation to the EML
- Rifampicin – addition of IV formulation to the EML

We are hereby providing our inputs and comments on the above-mentioned applications:

- **Bedaquiline – addition of 20 mg tablet formulation to the EML and EMLc, submitted by Janssen Pharmaceutica N. V.**

a) Bedaquiline is a key component of all-oral multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) treatment regimens, including the all-oral shorter regimen (for those eligible) and longer regimens. Indeed, bedaquiline is currently listed among the drugs to be prioritized for use in longer regimens for the treatment of MDR/RR-TB in adults and children (as one of three group A drugs). Current WHO guidelines recommend the use of bedaquiline for children aged 6 years and above.[1] Children aged 6 years and above and weighing less than 30 kg should receive half the adult dosage of bedaquiline at 200 mg daily for two weeks then tapering down to 100 mg thrice weekly for the remainder of treatment.

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. In light of these findings, it has become even more important to include child-friendly formulations in the WHO EMLc, so that countries can promptly access them.[2]

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[1] WHO consolidated guidelines on tuberculosis: Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240007048).
[2] Step Up for TB: TB policies in 37 countries, 4th Ed. Geneva: Médecins Sans Frontières (MSF), Stop TB Partnership; 2020. Available from: https://msfaccess.org/step-tb-tb-policies-37-countries-4th-ed?utm_source=Twitter&utm_medium=Organic&utm_campaign=SUFT

Bedaquiline is already listed in the WHO EML and EMLc (complementary list of medicines for the treatment of MDR-TB), as 100 mg tablets. The bioavailability of the 100 mg tablet formulation was shown to be the same whether the tablet is taken whole, crushed, or suspended in water.[3] However, manipulation of adult formulations to fit pediatric needs is not ideal. The availability of a child-friendly formulation of bedaquiline that is palatable and that can be dispersed in a small volume of water and mixed with a beverage (e.g., water, milk products, apple juice) or soft food (e.g., yogurt, apple sauce, mashed banana or porridge) is a step toward further in improving treatment options for children with MDR-TB. The 20 mg dispersible formulation of bedaquiline offers this flexibility.

Studies evaluating the pharmacokinetics, safety and tolerability of bedaquiline over 24 weeks using the 20 mg bedaquiline formulation are underway where children aged 0 to 5 years are being enrolled. When the results of these studies will be available, dosing recommendations will be considered for younger children.

By the end of March 2021, 25 countries had already procured the bedaquiline 20 mg dispersible tablet from the Stop TB Partnership's Global Drug Facility (STBP GDF) after it was made available in their catalogue in June 2020,[4] indicating that there is demand for this formulation.

In view of the above, **GTB supports** the inclusion of the bedaquiline 20 mg dispersible tablet on the complementary list of MDR-TB drugs in the WHO EMLc.

b) Based on current dosage recommendations in adult patients (see table below, as reported in the application by Janssen Pharmaceutica N.V.), using the 20 mg bedaquiline formulation to dose adult patients would result in a much higher number of tablets to be administered when compared with using the 100 mg tablet formulation (e.g., in the first two weeks of treatment 20 tablets instead of 4 daily), with corresponding cost implications. The 100 mg tablet formulation is currently priced at ~1,45 USD/tablet when procured from the STBP GDF, while the 20 mg tablet formulation is priced at ~0,43 USD/tablet. The cost for a six-month bedaquiline course for adults corresponds to ~270 USD[5] and ~400 USD[6] when using the 100 mg and 20 mg tablets, respectively. Considering that bedaquiline is only one component of MDR/RR-TB treatment regimens, the use of the 20 mg bedaquiline tablet for adult patients instead of the 100 mg tablet formulation would result in much higher costs, and it would likely not be acceptable given the perceived pill burden.

Table 1: Recommended Dosage of bedaquiline In Adult Patients[#]

Dosage Recommendation	
Weeks 1 and 2	**Weeks 3 to 24[a]**
400 mg (4 of the 100 mg tablets OR 20 of the 20 mg tablets) orally **once daily**	200 mg (2 of the 100 mg tablets OR 10 of the 20 mg tablets) orally **three times per week**
a = At least 48 hours between doses	
The total duration of treatment with bedaquiline in adults is 24 weeks. Bedaquiline tablets are administered with food.	

[#] US PI (40)

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[3] Svensson EM, du Bois J, Kitshoff R, de Jager VR, Wiesner L, Norman J et al. Relative bioavailability of bedaquiline tablets suspended in water: Implications for dosing in children. Br J Clin Pharmacol. 2018;84(10):2384–92 (https://dx.doi.org/10.1111/bcp.13696).

[4] Information provided by the STBP GDF.

[5] Médecins Sans Frontières Access Campaign, DR-TB & TB-Prevention drugs under the microscope, 7th edition, October 2020 (https://msfaccess.org/sites/default/files/2020-10/MSF-AC_IssueBrief_UTM_7th-Ed_2020.pdf)

[6] The cost for the six-month bedaquiline course for adults using the 100 mg and 20 mg tablet formulation were calculated based on dosages recommendations as in Table 1. The cost for a six-month bedaquiline course for adults using the 100 mg tablet formulation was cross checked with the cost reported by MSF in the "DR-TB & TB-Prevention drugs under the microscope, 7th edition" and takes into account

Even though the bedaquiline 20 mg tablet is also indicated for adults and/or adolescents who have trouble swallowing, there is insufficient justification that this specific formulation is essential for dosing in these groups. This also holds true considering the results of the Bedaquiline Crush study.[7] Where the 100 mg bedaquiline formulation may be exceptionally manipulated to enable appropriate dosing for adults and/or adolescents who cannot swallow, the study assessed that bioavailability is not altered with respect to whole tablets. It is anticipated that this is a small patient group.

In view of the above, GTB **does not support** the inclusion of Bedaquiline 20 mg dispersible tablet on the complementary list of MDR-TB drugs in the WHO EML.

c) The 20 mg tablet formulation of bedaquiline was approved by the US Food and Drug Administration (FDA) in 2020 for use in the population aged 5 years and older and weighing at least 15 kg.[8] The evidence on safety and effectiveness of bedaquiline use in patients below the age of 6 years was not available for review by the guideline development group convened by WHO in 2018. Therefore, current WHO guidelines, released in 2019 and further consolidated in 2020, recommend the use of bedaquiline for children aged 6 years and above.[9] We strongly encourage the alignment of the WHO EMLc with WHO Guidelines, and therefore recommend not to change the age cutoff reported for bedaquiline 100 mg in the WHO EMLc, so as to align with current WHO recommendations.

We would also like to note that GTB is undertaking an update of the guidelines on the management of TB in children, published in 2014.[10] Additional data that have become available since 2018, including data on the use of bedaquiline from younger cohorts from Janssen trial C211 and IMPAACT trial P1108 will be reviewed by the guideline development group and may prompt a change in WHO recommendation for the use of bedaquiline in children below the age of 6 years, which should be considered during the next update of the WHO EML and EMLc in 2023.

In view of the above, **GTB does not support** the proposal to lower the current age recommendation to children ≥ 5 years old and weighing at least 15kg for the bedaquiline 100 mg oral tablet in the EMLc.

- **Pyrazinamide – addition of 500 mg oral formulation to the EML, submitted by Dr. Jennifer Furin (Harvard Medical School, Boston, USA) and Brian Kaiser (Stop TB Partnership Global Drug Facility, Geneva, Switzerland), in collaboration with the TB Procurement and Market-Shaping Action Team (TPMAT)**

Pyrazinamide is a core therapeutic agent for all forms of TB and several pyrazinamide formulations are already currently listed in the WHO EML, namely:

- Oral liquid: 30 mg/mL [c]
- Tablet: 400 mg
- Tablet (dispersible): 150 mg
- Tablet (scored): 150 mg

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[7] Svensson EM, du Bois J, Kitshoff R, de Jager VR, Wiesner L, Norman J et al. Relative bioavailability of bedaquiline tablets suspended in water: Implications for dosing in children. Br J Clin Pharmacol. 2018;84(10):2384–92 (https://dx.doi.org/10.1111/bcp.13696).
[8] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204384s013lbl.pdf
[9] WHO consolidated guidelines on tuberculosis: Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240007048).
[10] http://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf?sequence=1

The addition of the 500 mg strength of pyrazinamide tablets would complement the 400 mg formulation that is currently listed, favouring adherence to treatment by reducing the pill-burden. This is particularly relevant in TB, where treatment is usually provided with patient support measures in place (i.e. directly-observed therapy, material or psychological support etc). Indeed, poor adherence, missed doses or early discontinuation of treatment due to a high pill burden and the long duration of treatment can have a major impact on treatment success.

For the treatment of drug-susceptible TB, pyrazinamide is recommended as part of a four-drug regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol and the recommended dose for the intensive phase of treatment for adults (2-3 months) is 25 mg/kg (20-30 mg/kg)[11]. As an example, an adult weighing 60 kg would take 3x500 mg tablets daily *versus* 4x400 mg tablets daily. This is particularly relevant for people who cannot use the preferred fixed-dose combinations of first-line medicines (e.g., people living with HIV on protease inhibitors, with drug-drug interactions with the rifampicin component of the FDC).

Pyrazinamide is also a key drug in regimens to treat patients with rifampicin-susceptible and isoniazid-resistant TB, as well as multi-drug resistant (MDR-)TB. For the treatment of MDR-TB, pyrazinamide is recommended both as part of a standard, shorter regimen (for those eligible) as well as in longer regimens for those who are not eligible for the shorter regimen. As shown in the Table below (*Dosing of medicines used in second-line multidrug-resistant-TB regimens by weight band (patients 15 years or older)*),[12] by using the 500 mg pyrazinamide tablets, the pill burden is reduced.

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients 15 years or older[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
	Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	5	–	
			500 mg tab	2	3	3	3	4		

Quality-assured formulations of pyrazinamide 500 mg tablets are available from the Stop TB Partnership Global Drug Facility (GDF),[13] and three suppliers of this formulation are currently prequalified by the WHO Prequalification of Medicines Programme.

Given the current price of the 400 mg and 500 mg tablets (comparable and, in some cases cheaper for the 500 mg tablets) and the reduced pill burden, cost savings are expected when using the 500 mg pyrazinamide formulations as well.

In view of the above, **GTB supports** the inclusion of Pyrazinamide 500 mg tablet to the EML.

- **Ethambutol – addition of IV formulation to the EML, submitted by INCURE CU;**
- **Isoniazid – addition of IV formulation to the EML, submitted by INCURE CU;**
- **Rifampicin – addition of IV formulation to the EML, submitted by INCURE CU;**

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[11] WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Annex 6, Essential fist-line antituberculosis drugs (https://www.who.int/tb/publications/2017/tb_guidelines2017_annex6_en_v4.pdf?ua=1)
[12] WHO operational handbook on tuberculosis: Module 4: Treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/9789240006997).
[13] GDF Medicines Catalogue. Geneva: Stop TB Partnership Global Drug Facility; 2020. Available here: http://www.stoptb.org/assets/documents/gdf/drugsupply/GDFMedicinesCatalog.pdf

We would like to note that these applications had been already submitted for inclusion in the WHO EML in 2019 by INCURE CU and at that time, they were reviewed by GTB. It should be noted that no major additions, especially in terms of available evidence to support the use of IV formulations for first-line TB medicines or information on market availability of these formulations, were included in the 2021 applications. We would also like to emphasize that no GTB staff member was consulted to review and support these applications in 2020-2021.

As highlighted in the memo "Comments to applications for updating of section 6.2.4 (antituberculosis medicines) in the Model list of Essential Medicines and the Model List of Essential Medicines for Children", dated 11 March 2019,[14] GTB did not support these applications in 2019. The same rationale described in 2019 applies. Indeed, WHO recommends oral treatment regimens for both patients with drug-susceptible and drug-resistant (rifampicin-resistant and multidrug-resistant) TB, as preferred options. GTB also highlighted that the majority of patients listed in the application – patients with severe forms of TB, patients with severe comorbidities and patients who are unable to take drugs – can be treated with oral formulations, if necessary, using alternative forms of administration. It is also stressed that for adult patients with drug-susceptible TB, a four-drug regimen including isoniazid, ethambutol, rifampicin and pyrazinamide is recommended, therefore patients on drug-susceptible TB treatment would still need to take pyrazinamide orally.

In 2019, the Expert Committee did not recommend the addition of IV formulations of ethambutol, isoniazid and rifampicin to the EML and EMLc for the treatment of drug-susceptible TB in combination with other first-line medicines. The Committee considered that the inclusion of these IV TB formulations on the EML could result in inappropriate use of IV therapy in patients otherwise able to take oral therapy. The Committee also noted the very limited marketed availability of these products, as well as a lack of information on comparative cost and cost-effectiveness.

In view of the above, GTB does not support the inclusion of the IV formulations of Ethambutol, Isoniazid and Rifampicin to the EML.

We thank you in advance for considering these inputs,

Dr Tereza Kasaeva

[14] https://www.who.int/selection_medicines/committees/expert/22/applications/s6.2.4_isoniazid-injection_GTBcomments.pdf?ua=1