# M E M O R A N D U M

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| **From:** Director, GTB | **To:** | Director, HPS | **Date:** **13 January 2021** |
| **Our ref:** | **Attention:** | Secretary of the Expert Committee on Selection and Use of Essential Medicines | |
| **Your ref:** | **Through:** | Unit Head, GTB/VCC | |
| **Originator: AB/TM/nb** | **Subject:** | **REMOVAL OF UNAVAILABLE OR UNAPPROPRIATE FORMULATIONS OF TB MEDICINES FROM THE WHO MODEL LISTS OF ESSENTIAL MEDICINES AND CONSOLIDATION OF AMIKACIN FORMULATIONS LISTED** | |

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The World Health Organization (WHO) Global TB Programme (GTB) acknowledges the key role that the WHO Model List of Essential Medicines (EML) and the WHO Model List of Essential Medicines for Children (EMLc) play in guiding countries and regional authorities to prioritize medicines for procurement in accordance with local public health needs and treatment guidelines. As the WHO EML and EMLc influence the medicines that people have access to, the contents of these lists constitute important determinants of health worldwide. It is therefore of the utmost importance that medicines, and corresponding formulations included in the WHO EML and EMLc align with most updated WHO clinical recommendations and reflect the latest developments in the availability of quality-assured formulations, including those that may be more appropriate for specific populations (e.g., children).

The WHO GTB and the Stop TB Partnership's Global Drug Facility (STBP's GDF) carried out a comprehensive review of the 2019 WHO EML and EMLc to examine the availability and appropriateness of the TB medicines and formulations included in both EMLs, in the context of the latest available WHO recommendations on TB and also procurement patterns, identifying unavailable or inappropriate formulations that are hereby being proposed for removal.

1. Formulations that are proposed to be **removed** from the **Core Lists** of both the WHO EML and EMLc (unless otherwise specified), are:

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| **Ethambutol** | Oral liquid: 25 mg/mL |
| **Isoniazid** | Oral liquid: 50 mg/5 mL |
| **Isoniazid** | Tablet (scored): 50 mg |
| **Pyrazinamide** | Oral liquid: 30 mg/ mL |
| **Pyrazinamide** | Tablet (scored): 150 mg |
| **Isoniazid + Pyrazinamide + Rifampicin**[(a)] | Tablet: 75 mg + 400 mg + 150 mg |
| [(a)] This fixed dose combination (FDC) tablet is not present in the WHO EMLc, therefore it is only submitted for removal from the WHO EML. | |

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**Rationale (for 1):** In 2019, the Committee recommended that several new formulations of medicines for use in children, including ethambutol (100 mg dispersible tablet) and isoniazid (100 mg dispersible tablet) be added to the Core Lists of the WHO EML and EMLc. The Committee did not recommend the addition of a new strength formulation of isoniazid oral liquid, acknowledging that quality-assured dispersible tablet formulations of TB medicines represent a preferred treatment option to oral liquid formulations. The Committee also recommended that oral liquid formulations of isoniazid and ethambutol be considered for removal from the WHO EML and EMLc in 2021 (see page 112 of the Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019).[1]

In line with the Committee recommendations and considering that dispersible tablet formulations of ethambutol and isoniazid have been available from the STBP's GDF since January 2018 and March 2019, respectively, and that dispersible tablets of pyrazinamide have been available from STBP's GDF since March 2018, we propose removal of the oral liquid formulations of Ethambutol, Isoniazid and Pyrazinamide from the WHO EML and EMLc. It should also be noted that there are currently two suppliers for WHO-Prequalified (PQed) pyrazinamide 150 mg dispersible tablet, and one for ethambutol and isoniazid, with a second one in the pipeline.

Acknowledging the preference for child-friendly, dispersible formulations of TB medicines, the removal of non-dispersible formulations of isoniazid and pyrazinamide that do not have any added value for dosing purposes (ie, isoniazid, tablet (scored): 50 mg; pyrazinamide, tablet (scored): 150 mg), is also proposed.

The fixed-dose combination (FDC) Isoniazid + Pyrazinamide + Rifampicin (Tablet: 75 mg + 400 mg + 150 mg) is also proposed for removal from the WHO EML, given that no quality-assured supplier of this formulation has been identified and that Ethambutol-containing FDCs (i.e., Ethambutol + Isoniazid + Pyrazinamide + Rifampicin, tablet: 275 mg + 75 mg + 400 mg + 150 mg; Ethambutol + Isoniazid + Rifampicin, tablet: 275 mg + 75 mg + 150 mg) are already listed in the WHO EML, which allow for a lower pill burden for the treatment of drug-susceptible (DS-)TB in adults.[2] Indeed, WHO recommends the use of FDC tablets over separate drug formulations in the treatment of patients with DS-TB.

2a. Formulations that are proposed to be **removed** from the **Complementary Lists** of the WHO EML and EMLc are:

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| **Amikacin** | Powder for injection: 100 mg |
| **Amikacin** | Powder for injection: 500 mg |
| **Amikacin** | Powder for injection: 1 g (as sulfate) in vial |
| **Amoxicillin/Clavulanic Acid** | Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL; |
| **Ethionamide** | Tablet: 125 mg |
| **Linezolid** | Injection for intravenous administration: 2 mg/ mL in 300 mL bag |
| **Linezolid** | Tablet: 400 mg |
| ***p*-aminosalicylic acid** | Tablet: 500 mg |

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[1] The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021). Licence: CC BY-NC-SA 3.0 IGO.

[2] Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

It should be noted that the proposed removals apply only to medicines/formulations that are listed in the WHO EML and EMLc in section *6.2.5 Antituberculosis medicines*. We propose no changes to Linezolid (injection for intravenous administration: 2 mg/mL in 300 mL bag) listed in section 6.2.3 (Complementary List) of the WHO EML and EMLc under *Reserve group antibiotics,* and Amoxicillin/Clavulanic Acid (Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL), listed in section 6.2.1 of the WHO EML and EMLc under *Access group antibiotics*

2b. Formulations that are proposed to be **added** to the **Complementary Lists** of the WHO EML and EMLc are:

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| **Amikacin** | Injection: 250 mg (as sulfate)/mL in 2- mL vial |

It should be noted that this formulation of Amikacin is already listed in the WHO EML and EMLc in section *6.2.1 Access group antibiotics*.

**Rationale (for 2a and 2b):** No quality-assured marketed formulations of Amikacin (powder for injection, 1 g (as sulfate) in vial), Linezolid (tablet: 400 mg) and *p*-aminosalicylic acid (tablet: 500 mg) have been identified, therefore these formulations are proposed for removal.

Since December 2019, WHO have recommended all-oral regimens, either long or short, to treat patients with drug-resistant (DR-)TB.[3] As well, the injectable agents Kanamycin and Capreomycin are no longer recommended as treatment options for drug-resistant (DR-)TB and in 2019 they were removed from the WHO EML and EMLc. While Amikacin is still included in the WHO grouping of medicines recommended for use in longer MDR-TB regimens, it is classified as a Group C drug (i.e., a drug to add to complete the regimen and when medicines from Groups A and B cannot be used). Amikacin is also not a medicine included in the shorter treatment regimens for DR-TB. Considering the foreseen limited use of Amikacin in the future, we propose: a) removing Amikacin, powder for injection (100 mg), considering the low efficiency in dose delivery, as a significant number of vials of this formulation would be required to reach the desired dose in adults and children; b) removing Amikacin, powder for injection (500 mg and 1 g) given that these formulations require reconstitution, and are therefore less ideal than a liquid formulation in resource-limited settings, and c) adding Amikacin, Injection: 250 mg (as sulfate)/mL in 2- mL vial to the Complementary List of section *6.2.5 Antituberculosis medicines* of the WHO EML and EMLc, noting that this liquid formulation, which is more adaptable to resource-limited settings, is the formulation available from the STBP's GDF and is already listed in the WHO EML and EMLc, in section *6.2.1 Access group antibiotics*.

Given the inclusion of solid oral formulations of linezolid in the WHO EMLs, including a 150 mg dispersible tablet, and considering WHO recommendations for all-oral regimens to treat patients with DR-TB, we also propose removal of Linezolid, injection for intravenous administration: 2 mg/ mL in 300 mL bag from the Complementary List of section *6.2.5 Antituberculosis medicines* of the WHO EML and EMLc.

Ethionamide tablet: 125 mg is proposed to be removed from the WHO EML and EMLc given the availability and listing of a corresponding dispersible tablet formulation in the WHO EML and EMLc, that has been available from the STBP's GDF since March 2018 from two suppliers that received WHO Prequalification status for this drug. It should also be noted that the price of the dispersible tablet formulation is comparable to the non-dispersible one.

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[3] 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, accessed 9 December 2020).

To consolidate the TB market around a specific formulation of Amoxicillin/Clavulanic Acid for children and considering that it is only recommended for use in combination with meropenem or imipenem+cilastatin, Amoxicillin/Clavulanic Acid, Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL is proposed for removal from the EML and EMLc in the section *6.2.5 Antituberculosis medicine*. It should also be noted that the oral liquid formulation 250 mg amoxicillin + 62.5 clavulanic acid/5 mL, which is already listed in the WHO EML and EMLc and is included in the dosing schemes of the WHO Operational Handbook on TB (Module 4: treatment – drug-resistant tuberculosis treatment)[4] enables appropriate dosing of children across age groups, while the formulation that we propose for removal would result in higher volumes to be administered.

3. Additional changes proposed by WHO GTB and STBP's GDF include to **list specific formulations for isoniazid and ethambutol rather than strength ranges**. Modifications proposed in the WHO EML and EMLc are listed below:

| | **WHO EML Current listings** | **WHO EML Proposed changes** | | **WHO EMLc Current listings** | **WHO EMLc Proposed changes** |
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| **Ethambutol** | Tablet: 100 mg to 400 mg (hydrochloride) | Tablet: 100 mg; 400 mg (hydrochloride) | | Tablet: 100 mg; 400 mg (hydrochloride) | *None*[(b)] |
| **Isoniazid** | Tablet; 100 mg to 300 mg | Tablet: 100 mg; 300 mg | | Tablet; 100 mg to 300 mg | Tablet: 100 mg; 300 mg |
| [(b)]It should be noted that Ethambutol is already listed as two separated formulations (100 mg; 300 mg) in the WHO EMLc | | | | | |

**Rationale (for 3)**: 100 mg (dispersible and non-dispersible) and 400 mg tablet formulations of Ethambutol allow to deliver appropriate dosing for adults and children with TB, as recommended by WHO. No quality-assured formulation is available on the market in the 100–400 mg strength range that could deliver an added value to dosing patients with TB. By removing the strength range for Ethambutol, we would also align with how Ethambutol is listed in the WHO EML and EMLc.
While a 200 mg tablet formulation of isoniazid is available on the market, which is approved by the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte or BfArM, i.e., the German Drug Regulatory Authority), this formulation does not have any added value in terms of facilitating dosing for adults or children. 100 mg (dispersible and non-dispersible) and 300 mg tablets of Isoniazid are the essential set of formulations that allow correct dosing for adults and children with TB.

Finally, please note that separate applications are being submitted by WHO GTB for the addition of an FDC of Rifapentine (300mg) and Isoniazid (300mg) as well as for the addition of Rifapentine 300 mg (scored tablet) to the core list of the WHO EML and EMLc. An application for the addition of Delamanid 25 mg dispersible tablets to the complementary list of the WHO EMLc is also being submitted (attached).

We thank you in advance for requesting that these changes be made to the WHO EML and the EMLc.

Dr Tereza Kasaeva

[4] 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, accessed 9 December 2020).