D.2	TB Formulations – deletions
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☐ No ☒ Not applicable Comments: The application is looking at Formulations that are proposed to be removed from the Core Lists of both the WHO EML and EMLc; formulations that are proposed to be removed from the Complementary Lists of the WHO EML and EMLc; formulations that are proposed to be added to the Complementary Lists of the WHO EML and EMLc; and to list specific formulations for isoniazid and ethambutol rather than strength ranges
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.	These medicines are already listed on the WHO EML and 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). 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:

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☒ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Not applicable
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Not Applicable
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:
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: Medicines are currently listed in the WHO EML and EMLc
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Different formulations and strengths are available in different countries at affordable prices.
Any additional comments	While fixed dose combinations (FDCs) have become the “norm” for TB therapy, there still is a need for individual agents to be available if patients are resistant or have side effects to individual agents within the combinations. Prescribers may also want to add individual agents to combinations in rare cases where patients are not responding to FDC therapy. In addition, the application makes reference to availability of quality assured products, but the reference is actually to the number of pre-qualified products by WHO, which should not be a reason for deletion of medicines from the WHO EML or EMLc. Countries may use different procurers based on what is available in their country. As such a range of formulations and strengths are required to allow countries to be able to purchase products registered for use in their country, and ensuring that a pool of suppliers exist, and no monopoly is created. This could impact on availability and affordability of TB medicines in the future.

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 reviewer recommends the following:

1. The following are **not removed** from the core list of the WHO EML and WHO EMLc

- 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 Tablet: 75 mg + 400 mg + 150 mg (EML only)

While new child friendly formulations may exist, these formulations are required for patients where dispersible/oral formulations will not work (i.e. through nasogastric tubes, etc.). In addition, in rare cases where individual agents are required to be added to existing FDCs, these agents will be required.

2. The following **be** removed for TB indication from the complementary list of WHO EML and WHO EMLc
    - Amoxicillin/Clavulanic Acid Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 mL
    - Linezolid Injection for intravenous administration: 2 mg/mL in 300 mL bag

Linezolid (injection for intravenous administration: 2 mg/mL in 300 mL bag) is 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), is listed in section 6.2.1 of the WHO EML and EMLc under Access group antibiotics.

3. The following **not removed** for TB indication from the complementary list of WHO EML and WHO EMLc

- Amikacin Powder for injection: 100 mg
- Amikacin Powder for injection: 500 mg
- Amikacin Powder for injection: 1 g (as sulfate) in vial
- Ethionamide Tablet: 125 mg
- Linezolid Tablet: 400 mg
- p-aminosalicylic acid Tablet: 500 mg

Different countries have access to different formulations (in terms of registration, affordability, and supply) and removing options may result in non-availability and the creation of monopolies of suppliers.

4. The use of specific formulations rather than strengths ranges is **not recommended** as presented by the applicant below:

	WHO EML Current listings	WHO EML Proposed changes	WHO EMLc Current listings	WHO EMLc Proposed changes
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

Different countries have access to different formulations (in terms of registration, affordability, and supply) and removing options may result in non-availability and the creation of monopolies of suppliers.

5. Addition of new formulation is recommended
    - Amikacin Injection: 250 mg (as sulfate)/mL in 2mL vial

Different countries have access to different formulations (in terms of registration and supply) and adding options may increase-availability and the pool of suppliers.

References (if required)	