Expert peer review on application for inclusion of a fixed-dose combination of isoniazid+pyridoxine+sulfamethoxazole+trimethoprim.

1. Assessment of efficacy

a. Have all relevant studies on efficacy been included
   Yes ✓  No (if no, please provide reference and information)

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The data on efficacy refer to the individual components, and to the prevention of the respective infections as well as HIV-related clinical outcomes, not to the efficacy of the proposed FDC per se.

c. Please provide any additional relevant information with reference

2. Assessment of safety

a. Have all relevant studies on safety been included
   Yes ✓  No (if no, please provide reference and information)

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

As with the efficacy data, those data on safety that are available have largely been generated from studies of the individual prophylactic regimens, not from the combined use of cotrimoxazole prevention therapy (CPT) and isoniazid prevention therapy (IPT). Nonetheless, the safety profiles of the component parts of the FDC are well characterised. While not common by any measure, the risks of severe cutaneous reactions, including Stevens-Johnson syndrome, with CPT do need to be taken into account.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability

a. Have all relevant data on cost and availability provided
   Yes ✓  No (if no, please provide reference and information)

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The available data refer only to the component parts, not to the FDC, which has yet to be produced commercially. Both CPT and IPT are widely accessible, if not as widely prescribed as they could be. The major
barriers here are health worker awareness, not the cost of the individual components. However, the extent to which the FDC would be procured is highly dependent on the price comparison relative to the individual components, and whether the anticipated adherence and programmatic advantages are considered worthwhile.

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

No. No registered product yet exists, even though the FDC has been included in the WHO PQ EoI list.

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

The public health need for widespread and effective access to CPT and IPT in areas of high HIV and TB burden has been clearly demonstrated. The provision of prophylactic pyridoxine to patients on INH therapy (both prophylactic and therapeutic) is also well established, although the dosages used vary widely.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Current guidance supports both CPT and IPT in such settings. These guidelines are expected to be updated as part of a comprehensive review of HIV guidance from WHO in 2013 (as part of the Treatment 2.0 initiative). All of the constituent elements of this proposed FDC are already included on the WHO Model EML. However, there are differences in the duration of both CPT and IPT in different settings, according to national guidelines. There will also be some patients who require CPT but not IPT, or vice versa, and who will also not tolerate one or other and therefore need access to individual components. This is not, however, a problem that is unique to this FDC.

5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

No.

6. Is the proposed product registered by a stringent regulatory authority?

   Yes  No ✓

7. Any other comments

It appears from the application that bioequivalence studies of the proposed FDC formulation have not yet been conducted. This may well delay responses to the WHO PQ EoI and also applications to stringent regulatory authorities. The extent to which the final product will facilitate dosing in children is also unknown at this point, although the application does claim that scored tablets would be suitable (in ½ and ¼ portions).

8. What is your recommendation to the committee (please provide the rationale)

Although the public health arguments for increased use of FDCs to enhance compliance with recommended standard regimens and avoid prescriber error are compelling, much depends on the availability of a quality-assured and affordable commercial product for procurement by country programmes and donors. In this case,
no such product is yet commercially available. It could be argued, as was the case with oro-dispersible zinc sulphate tablets, that inclusion on the WHO Model EML could serve to stimulate the development of the market for such a product. That much seems already to have been achieved through the inclusion of this proposed FDC in the WHO PQ EoI lists. In contrast, the WHO EML should rather restrict itself to the inclusion of products that can be immediately added to country EMLs and that can be procured commercially, even if the number of suppliers remains limited at the time of inclusion. This would be consistent with the decision taken by the last Expert committee. TRS965 summarised the decision as follows: “The Committee noted that the product is not yet manufactured and no manufacturer has been identified. A report of a pharmaceutical feasibility study was provided that suggests the combination is technically feasible. There is no information about the potential cost of the combination product. Given the large amount of active pharmaceutical ingredients in the proposed FDC, formulation of an adequate product may result in a price that is higher than the existing loose combination. The Committee decided that as the product does not yet exist, it cannot be added to the EML. The Committee decided to include it on a list of ‘missing’ essential medicines. Given that the new WHO Guidelines also recommend isoniazid and cotrimoxazole prophylaxis in children with HIV, a paediatric strength product also should be developed. The dose of isoniazid should be 10 mg/kg per day and the dose of cotrimoxazole needs to be determined.” This application provides no additional information that can justify a different conclusion, and it is therefore recommended that the proposed inclusion not be approved. Instead, it may be preferable, at this stage, for the WHO Model List merely to include preventive therapies in the introductory text to the relevant sections. The following additions are suggested (underlined in bold type):

Section 6.2.4 Antituberculosis medicines

“The Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality. **The Committee also recommends the development of appropriate fixed-dose combination products for preventive use in persons living with HIV, including products for combined sulfamethoxazole/trimethoprim (cotrimoxazole) and isoniazid preventive therapy.**”

Section 6.4.2 Antiretrovirals

“Based on current evidence and experience of use, medicines in the following three classes of antiretrovirals are included as essential medicines for treatment and prevention of HIV (prevention of mother-to-child transmission and post-exposure prophylaxis). The Committee emphasizes the importance of using these products in accordance with global and national guidelines. The Committee recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality. **The Committee also recommends the development of appropriate fixed-dose combination products for preventive use in persons living with HIV, including products for combined sulfamethoxazole/trimethoprim (cotrimoxazole) and isoniazid preventive therapy.** Scored tablets can be used in children and therefore can be considered for inclusion in the listing of tablets, provided adequate quality products are available.”