(1) Does the application adequately address the issue of the public health need for the medicine?
   Yes ☒ No ☐
   Please provide brief details:

(2) Have all important studies that you are aware of been included in the application?
   Yes ☐ No ☒
   Please provide brief comments on any relevant studies that have not been included:
   They have omitted Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD007545. DOI: 10.1002/14651858.CD007545.pub2.
   They cite a JAMA network meta-analysis (Stagg et al., ref 35) but this does not deal with the Aes so well. The Cochrane review summarises all the data from the various publications of the one trial evaluating this. There is a balance between various AES, but importantly there is less hepatotoxicity with the shorter, rifapentine regimen. See annex.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes ☒ No ☐
   Briefly summarise the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine:
   Prevention of TB in people with LTBI

(4) Is there evidence of efficacy in diverse settings and/or populations?
   Yes ☒ No ☐
Please provide brief details: Maybe. Brazil, usa, Canada; and in HIV positive in South Africa. It isn’t clearly presented, but in HIV and negative. Children aged 2-11 were tested in S26 study with a total of 522, so the panel may wish to discuss safety in children.

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☐ No ☒

Please provide brief details:
The submission does not refer to the higher level of possible hypersensitivity with rifapentine reported in the supplementary information annex 11 of the network meta-analysis in Stagg and in the Cochrane review. The panel will need to discuss this.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☐ No ☒

Please provide brief details:

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☐

Please provide brief details: registered in USA but not elsewhere

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☒

Please provide brief details: WHO Guidelines for the management of latent tuberculosis infection was published in 2015 but the annexes are not available containing GRADE and the guideline is not listed on the GRC approved guidelines listing. This is a concern.
(9) Please comment briefly on issues regarding cost and affordability of this medicine.
Cost not fixed yet. Much development with public money. Cheaper delivery as shorter course.

(10) Any additional comments?
There is an a priori reason for concern over development of drug resistance as this drug has a long half-life. On page 22 this is considered. However, the submission wrongly attributes the conclusion that preventive regimens with the class of drugs of rifamycins did not contribute to resistance, but a) this does not deal with rifapentine as an individual drug; and b) this is a JUDGEMENT by the panel based on the GRADE and other information, not a fact derived from the systematic review.

(11) Please summarise the action you propose the Expert Committee takes.
The WHO should provide the GRADE tables referred to in the submission prior to the meeting. It would be helpful if WHO could clarify the GRC status of the latent TB guidelines.

The panel should discuss

- Hypersensitivity data.
- If approved, is it for adults only? Data on children is limited.
- The specific contribution of this drug to drug resistance.

On the whole though this drug has a number of substantive advantages.

Paul Garner
Annex
Summary from Cochrane review

The combination treatment was associated with significantly fewer severe adverse events (1.6%) than INH alone (2.8%) (RR 0.55, 95% CI 0.44 to 0.74; one trial, 7799 participants, Analysis 4.5).

However, more people receiving the combination treatment had treatment-limiting adverse events that led to permanent discontinuation (4.9%) compared to those on INH alone (3.7%) (RR 1.32, 95% CI 1.07 to 1.64; one trial, 7731 participants, Analysis 4.6).

The rifapentine combination was also associated with more frequent symptoms that were considered possible hypersensitivity reactions (3.8%) than with INH alone (0.5%) (RR 8.32, 95% CI 5.05 to 13.71; one trial, 7799 participants, Analysis 4.7). Six of the 152 people with possible hypersensitivity reactions had hypotensive episodes.

The combination resulted in significantly fewer instances of severe hepatotoxicity (0.4%) than with INH given for nine months (2.7%) (RR 0.16, 95% CI 0.10 to 0.27; one trial, 7799 participants, Analysis 4.8).

The interventions did not significantly differ in producing a rash (one trial, 7799 participants, Analysis 4.9).

Of the 7799 subjects who received at least one dose of a study drug, 1062 (13.6%) had one adverse event, and 194 (2.5%) had more than one adverse event. Overall, there was a small but statistically significant excess in the proportions on INH alone (17.6%) who reported any adverse event than on the rifapentine plus INH combination (14.7%) (RR 0.84, 95% CI 0.76 to 0.93; one trial, 7799 participants, Analysis 4.10).

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