(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:

The systematic review by Sotgiu et al 2012 is referenced but the data contained in the review is not referred to or used well.

The critical issue with the off-label use of this drug for TB is the AES. These appear substantive, but are not captured in the submission provided.

(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:

I don’t think the submission adequately summarises the AES. The GRADE analysis and tables are not well synthesised. The committee needs to consider Sotglu’s analysis, which is helpful.

(4) Is there evidence of efficacy in diverse settings and/or populations?
   Yes ☒  No ☐

Please provide brief details:
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  ☐

There is a clearly expressed urgency with statements about mortality from MDR TB, lack of options, need to urgently introduce these “life-saving” drugs to add to current “archaic” options. Whilst I understand these concerns, there is little attention to adequate monitoring of adverse effects on the ground. Maybe this is contained in the SOPs for the specialised centres.

ADDITIONAL CONSIDERATIONS:

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

Yes  ☒  No  ☐

Please provide brief details: The application states: “Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDRTB) should be used in specialized centres adhering to WHO standards for TB control.”

It would be helpful to be clear from WHO what this means and how it will be assured.

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:
Off-label use

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

Yes  ☐  No  ☒

Status unclear

Please provide brief details:
It is not clear if the book, “Companion handbook to the WHO guidelines for the programmatic management of drug resistant TB (WHO/HTM/TB/2014.11) IS GRC APPROVED. It is not currently on the WHO site of GRC approved guidelines. It would be helpful if WHO could clarify the position.
(9) Please comment briefly on issues regarding cost and affordability of this medicine.
There appears to be a reasonably priced generic and others in the pipeline.

(10) Any additional comments?

(11) Please summarise the action you propose the Expert Committee takes.

The panel needs to consider the adequacy of patient monitoring and appropriate use of this drug before approval. There is information about the status of the drug resistant guideline and the level of care provided at the WHO recommended centres.
Annex 1. Extract from abstract, and adverse events from Sotgiu (2012)

Most MDR-TB cases achieved sputum smear (86 (92.5%) out of 93) and culture (100 (93.5%) out of 107) conversion after treatment with individualised regimens containing linezolid (median (inter-quartile range) times for smear and culture conversions were 43.5 (21–90) and 61 (29–119) days, respectively) and 99 (81.8%) out of 121 patients were successfully treated. No significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage ≤ 600 mg versus > 600 mg). Adverse events were observed in 63 (58.9%) out of 107 patients, of which 54 (68.4%) out of 79 were major adverse events that included anaemia (38.1%), peripheral neuropathy (47.1%), gastro-intestinal disorders (16.7%), optic neuritis (13.2%) and thrombocytopenia (11.8%). The proportion of adverse events was significantly higher when the linezolid daily dosage exceeded 600 mg.

The study results suggest an excellent efficacy but also the necessity of caution in the prescription of linezolid.

| TABLE 6 | Retrospective evaluation of the safety and tolerability of linezolid in 121 multidrug-resistant tuberculosis cases |
|-------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------|-----------------|
| Patients exposed to LNZ | Total | LNZ daily dose ≤ 600 mg | LNZ daily dose >600 mg | p-value |
| Adverse events attributed to LNZ | 63/107 (58.9) | 28/60 (46.7) | 35/47 (74.5) | 0.004 |
| Major adverse events | 54/107 (61.1) | 27/44 (61.4) | 27/33 (77.1) | 0.14 |
| Anaemia | 32/84 (38.1) | 11/49 (22.5) | 21/35 (60.0) | 0.0006 |
| Leukopenia | 7/85 (8.2) | 1/50 (2.0) | 6/35 (17.1) | 0.012 |
| Thrombocytopenia | 10/85 (11.8) | 5/50 (10.0) | 5/35 (14.3) | 0.55 |
| Peripheral neuropathy | 40/85 (47.1) | 20/50 (40.0) | 20/35 (71.1) | 0.12 |
| Optic neuritis | 10/76 (13.2) | 4/41 (9.8) | 6/35 (17.1) | 0.35 |
| Gastro-intestinal disorders | 14/84 (16.7) | 4/90 (8.0) | 10/34 (29.4) | 0.01 |
| Exposure to LNZ days | 300 (143–690) | 589.5 (154.5–750) | 292 (120–440) | 0.03 |

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. LNZ: linezolid.