Does the application adequately address the issue of the public health need for the medicine?

Yes ☐ No ☐

Please provide brief details:
Tuberculosis continues to be a prevalent disease. The number of MDR-TB/RR_TB and XDR-TB continues to increase. The treatment for these patients is complex, resulting in low adherence. Due to this, developing new treatment options and creating new regimens that are more amenable is a priority.

Have all important studies/evidence of which you are aware been included in the application?

Yes ☐ No ☐

Please provide brief comments on any relevant studies that have not been included:
A prospective cohort study evaluated patients with a diagnosis of XDR-TB in South Africa for around 4 years. It showed that clofazimine was an independent predictor for net culture conversion (p=0.0069) and survival (p=0.021)\(^1\).

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☐ No ☐

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

A RCT published on 2015 (reference 26) showed higher success rate and earlier resolution of disease markers on patients receiving Clofazimine. Unfortunately, this study had a small sample size (N=105 patients) and presented significant risk of bias; no placebo was given, there was no blinding and clofazimine group received one more drug (6 instead of 5 in the control group). Additionally, the outcome “treatment success” is a composite outcome that includes “cure” and “treatment completion”. Cure rate as an independent outcome wasn’t statistically significant: 27 (50.9%) vs. 20 (38.5%) p= 0.20. On the other hand, clofazimine did not improve death rate (7.5% vs. 7.7%, p=1). Earlier sputum culture conversion in patients was seen in patients assigned to clofazimine group (P =.042 by log-rank test).
Two systematic reviews (Reference 24 and 25) evaluated the efficacy and safety of clofazimine. They included uncontrolled observational studies. They did not compare clofazimine to the optimized standard regimen. Both reviews present very low quality when assessed according to GRADE approach.

- **Dey 2013** included 12 cohort studies, most of them retrospective or unknown. Included studies were highly heterogeneous in terms of dose, length of treatment and underlying HIV status. Included studies presented moderate to high risk of bias according to modified New Castle-Ottawa scale. They reported that the overall pooled proportion of treatment success was 61.96% (95% CI 52.79%–71.12%) (τ² 0.07), treatment success was defined as “cure” and “treatment completion” making the evaluation of this outcome complicated. Cure is not reported independently.

- **Gopal 2013** included 9 observational studies. No quality evaluation of these studies is included in the review. Studies were highly heterogeneous. This review found that 65% (95%CI 54–76) of all patients treated with clofazimine-containing regimens experienced favorable outcomes (defined as “cure” and “treatment completion”). In stratified analysis, 65% (95%CI 52–79) of those with MDR-TB and 66% (95%CI 42–89) of those with XDR-TB experienced favorable treatment outcomes. Cure is not reported independently.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:
No. Taking the limitations of the available studies (described above) I don’t think there’s enough evidence available to conclude with certainty the efficacy of clofazimine in the treatment of drug resistant TB.

(4) 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 [x]

Please provide brief details:
Most of the evaluated studies reported mild side effects, mainly related to the GI tract. Discoloration of skin, mucosa and body fluids is reversible over time. These side effects did not lead to treatment discontinuation in a significant number of patients (<1% of patients). Additionally, Clofazimine has been use since 1962. The associated adverse drug reactions have been described since 1962, when it entered the market, through its’ use for the management of leprosy.

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).
I consider that clofazimine is a safe medication but it’s benefits for the management of MDR and XDR-TB are not clear and more research to clarify its’ role is needed.
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:
   Clofazimine has been approved for multiple agencies for a long time but not for its use in TB.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?
   Yes ☐ No ☐

   Please provide brief details:
   Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update

(9) Please comment briefly on issues regarding cost and affordability of this medicine.
   No cost-effectiveness analysis has been developed.
   The cost of this medicine is for 100mg: $109.48–126.72/100cap

(10) Any additional comments?
   -

(11) Please frame the decisions and recommendations that the Expert Committee could make.
   There is not enough evidence to support the effectiveness of clofazimine in the treatment of MDR/XDR TB.

(12) References (if required)