2019 Expert Committee on Selection and Use of Essential Medicines

Peer Review Report

[Delaminid]

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

Yes ☑️ No ☐

Please provide brief details: Proven effective adjunct oral medicine for RR/MDR-TB based on adult and limited pediatric data.

(2) 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: TAG group refers to emerging data which to date, are not available in peer-reviewed medical literature. Largest existing database appears to be internal data from Otsuka upon which current WHO recommendations appear to be based. A review of current published medical literature (PubMed) revealed no published information on the pharmacokinetics (metabolism), pharmacodynamics or bioavailability information in young children.

(3) 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: Although not contained in the application for lowering the age-restriction, therapeutic benefit clearly established from adult studies of RR/MDR-TB. With regard to safety considerations surrounding injectable alternatives which are significant in pediatric populations (e.g., hearing loss), availability of an oral adjunctive treatment is essential.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details: Yes, clearly in adult patients. There are published (and anecdotal) reports suggesting the efficacy and safety of delaminid in children > 6 years of age.
(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 ☐

Please provide brief details: Application per se does not focus on safety or adverse effects. However, QTc prolongation associated with Delaminid has been reported and it is not known whether infants or young children, especially those with malnutrition and potential electrolyte disturbances associated with nutrition and/or concomitant disease conditions (e.g., infectious diarrhea with dehydration) would impact the susceptibility of this particular adverse event. Thus, clinicians must be aware and consider special monitoring if they believe a patient is “at risk”.

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc). In patients with RR/MDR-TB who require add-on therapy and for whom parenteral treatment is not possible and/or associated with greater risk of adverse effects, the overall benefit of Delaminid appears to outweigh the risks in children >6 years of age (based on limited available data to date).
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: Decision to use the medication in children <6 years of age should involve consultation with paediatricians skilled in treating RR/MDR-TB. Follow-up of patients receiving the drug should be performed by physicians skilled in detecting and treating drug-related adverse effects (e.g., QTc prolongation).

(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: Expanding the approved product labelling for children will require completion of well controlled, appropriately designed clinical trials (e.g., longitudinal assessment of add-on treatment). Also, expanded product labelling must include data on pharmacokinetics and dose selection (e.g., exposure-response data) in pediatric patients. Many agencies will allow inclusion of adverse events that are published in the peer-reviewed literature and this should be considered, especially for cardiac rhythm disturbances. Finally, for the new oral dispersable formulations of the drug, appropriate relative bioavailability studies must be performed (preferably in children).

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

Please provide brief details: Yes. In 2018 guidelines

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

Based on recent information (Gotham D, et al. J Antimicrob Chemother 2017;72: 1243-1252), estimated generic prices for Delaminid are $4-$16 (USD) per month and that for a Delaminid-based 4 drug regimen are $238-$507 per month. Estimated generic prices for Delaminid are reported to be 95-98% lower than the current lowest available prices for brand name product. Affordability of Delaminid to developing or resource constrained countries could well pose economic challenges.
(10) Any additional comments? None

(11) Please frame the decisions and recommendations that the Expert Committee could make.

Consideration can be given to lowering the age-range for Delaminid to greater to or equal than 3 years of age for children with no evidence of hepatic or renal impairment or significant under-nutrition. It should be denoted that this “recommendation” is not based on published data describing the disposition, safety or efficacy of this drug in children < 6 years of age but rather, it is based upon the fact that consideration of the absorption, distribution, metabolism and excretion of the drug should be “functionally mature” in children 3 years of age or greater. Consequently, allometric scaling of the dose to children down to 3 years of age should be possible based on known pharmacokinetic and pharmacodynamic data.

(12) References (if required)

