South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Respiratory

MEDICINE REVIEW:

1. Executive Summary

Date: 13 June 2019
Medicine (INN): Delamanid, oral
Medicine (ATC): J04AK06
Indication (ICD10 code): Multi Drug-Resistant tuberculosis [A15-A19 + (U50.00-01)]
Patient population: Adults with rifampicin-resistant tuberculosis
Prevalence of condition: 2.8% of new TB cases are multidrug-resistant in South Africa.[1]
Level of Care: Primary health care
Prescriber Level: Medical Officer
Current standard of Care: ≥5 drug MDR TB regimen.
Efficacy estimates: (preferably NNT): NNT = 7 for 1 additional culture conversion at 2 months.
Motivator/reviewer name(s): Dr J. Nel, Mr R Wiseman
PTC affiliation: n/a

2. Name of author(s)/motivator(s)

Primary reviewer: Dr Jeremy Nel
Secondary reviewer: Mr Roger Wiseman

3. Author affiliation and conflict of interest details

Dr J Nel:

- *Affiliation:* University of the Witwatersrand; Co-opted expert to the Adult Hospital Level Committee (2017-2020)
- *Conflict of interests:* AbbVie (Consultation on ARV study); Helen Joseph Hospital (Cryptococcal meningitis research); Mylan (Consultation on ART regimens)

Mr R Wiseman

- *Affiliation:* Liberty Health Cover Medical Scheme, Vice-chair of the Tertiary/Quaternary Expert Review Committee and Member of the National Essential Medicines List Committee
- *Conflict of interests:* None declared

4. Introduction/ Background

Multidrug resistant (MDR) tuberculosis (TB), defined as tuberculosis resistant to both isoniazid and rifampicin, accounts for approximately 2.8% of tuberculosis cases in South Africa, and the prevalences of the closely-related rifampicin-monoresistant, pre-extensively-drug resistant (XDR) and XDR strains.[1] In many such cases, the patient's TB strain may be resistant to one or more of the second-line drugs conventionally used to treat MDR TB. In addition, treatment success rates with the current standard of are regimen are suboptimal, owing to several of the constituent drugs having only marginal efficacy and/or poor side-effect profiles. Only approximately 22% of rifampicin-resistant TB cases successfully complete treatment in South Africa.[2] Thus, there is a substantial need for novel drugs that have better efficacy and/or improved safety. Delamanid is a novel antituberculous agent that has been touted as a drug to either add to existing regimens for drug-resistant TB or replace one or more of the existing drugs in these treatment regimens.

5. Purpose/Objective i.e. PICO

-P: adult patients with rifampicin-resistant tuberculosis
-I: use of delamanid as part of multi-drug treatment regimen
-C*:* standard of care multi-drug treatment regimen
-O: efficacy: culture conversion, cure rate, mortality rate; tolerability: grade 3 and 4 adverse events, mortality rate

6. Methods:

a. Data sources PubMed, Cochrane, NIH

b. Search strategy

PubMed: (("OPC-67683"[Supplementary Concept] OR "OPC-67683"[All Fields] OR "delamanid"[All Fields]) AND ("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR ("tuberculosis"[All Fields] AND "tb"[All Fields]) OR "tuberculosis tb"[All Fields])) AND (Clinical Trial[ptyp] OR systematic[sb])

PubMed was searched for clinical trials, and systematic reviews, using the above search strategy, limiting search results to clinical trials or systematic reviews.

The Cochrane reviews were searched for reviews containing the terms “delamanid”, “tuberculosis”, and “TB”.
Lastly, clinicaltrials.gov was searched for any additional completed phase 3 RCTs that had not yet been published but that had results publicly available.

There were no applicable results found in the Cochrane reviews.

In PubMed, 13 studies were identified. 11 were rejected:

Study	Reason for rejection
Diacon AD et al. 2011	Early bactericidal study. No endpoints relevant to PICO analysis.
Zhang Q et al. 2013	Separate single-country subset of results from patients whose results were fully reported in a multi-country trial
Gupta R et al. 2015	Letter summarizing the delamamid evidence, but without new trial data.
Meng M et al. 2015	PK study, no study endpoints relevant to PICO analysis.
Tupasi T et al. 2016	Descriptive study of capacity building programs during delamanid trials.
Stinson K et al. 2016	PD study aiming to determine MICs for delamanid. Not relevant to PICO analysis.
Mallikaarjan S et al. 2016	PK study of drug-drug interactions with delamanid. Not relevant to PICO analysis.
Migliori GB et al. 2017	Systematic review of treatment using delamanid and bedaquiline together, rather than separately.
Pontali E et al. 2018	Systematic review of treatment using delamanid and bedaquiline together, rather than separately.
D’Ambrosio et al. 2017	Study in children, not adults
Harausz EP et al. 2018	Study in children, not adults

The remaining 2 trials were included (see below).

1 additional RCT was identified in clinicaltrials.gov, and was included (see below).

c. Evidence synthesis

Author, date	*Type of study*	*n*	*Population*	*Comparators*	*Primary outcome*	*Effect sizes*	*Comments*
A: RCTs							
Gler MT et al., 2012[3]	Phase 2b RCT – double-blind, placebo controlled. 3 arms: delamanid 100mg twice daily, delamanid 200mg twice daily, placebo.	481	Adults 18-64 with pulmonary rifampicin-resistant TB (defn: positive sputum culture for rifampicin-resistant TB and compatible chest X-ray findings). Enrolled from 17 countries (none in Africa).	Delamanid vs placebo, given for 2 months. (Both arms given on background of WHO-guideline-endorsed MDR TB regimen at the time).	Proportion of patients with culture conversion at 2 months.	45.4% culture conversion at 2 months, vs 29.6% with placebo (p = 0.008). Longer QT interval in delamanid groups.	Study added delamanid to background regimen, rather than replacing any of the drugs (potential to underestimate efficacy). Two different doses of delamanid were tested simultaneously, though not much difference between them. Focus was on pulmonary (not extra-pulmonary MDR TB). Important exclusions: poor baseline function (Karnovsky score <50%), HIV positive if CD4 <350, "clinically relevant" cardiovascular disease, prolonged QTc, etc.
von Groote-Bidlingmaier F et al., 2019[4]	Phase 3 RCT – double-blind, placebo-controlled	511 for safety analysis, 327 of whom were sputum positive and were used to determine efficacy.	Adults 18-69 years with pulmonary MDR TB, enrolled from 17 sites in 9 countries (including South Africa).	Delamanid for 6 months (200mg daily dose, given as 100mg bd for 2 months, then 200mg daily for 4 months) vs placebo. Both given in addition to optimized background MDR regimen.	Time to sputum conversion. Secondary outcomes included sputum conversion proportion, and treatment outcomes.	Efficacy: No statistically significant differences in time to sputum culture conversion (HR 1.17, CI .91-1.51), proportion of patients with sputum culture conversion at a variety of time points, treatment success at month 30 (RR 0.991, CI 0.872-1.127, p=0.90), 30 month all-cause mortality (RR 1.122, CI 0.498-2.527, p=0.78), 30-month TB-	Study added delamanid to background regimen, rather than replacing one of those drugs (potential to underestimate efficacy). Important exclusions: poor baseline function (Karnovsky score <50%), "cardiovascular conditions". HIV patients excluded from all sites except South Africa. Substantial involvement by Otsuka (delamanid manufacturer): "responsible for study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit for publication".

						related mortality (RR 1.496, CI 0.410-5.453, p=0.54). Safety: higher incidence of worsening of TB, hypokalaemia, QTc prolongation.	
B: Observational studies							
Wells C, et al. 2015[5]	Observational study – open label extension of Gler et al.'s RCT above. Some patients had subsequently received a further 6 months' delamanid as part of a separate trial. Formulated as a letter to the editor.	463 (of the 481 patients in Gler's trial above)	Adults 18-64 with pulmonary rifampicin-resistant TB (defn: positive sputum culture for rifampicin-resistant TB and compatible chest X-ray findings). Enrolled from 17 countries (none in Africa).	(1) Delamanid ≥6 months vs Delamanid ≤2 months. (2) Delamanid ≥6 months vs no delamanid.	Mortality at 24 months	(1) Patients with long-term delamanid had lower likelihood of mortality 2.9% vs 12.0% (OR 0.22, CI 0.09-0.54). (2) Mortality for patients receiving long-term delamanid 2.9% vs 14.5% if no delamanid. (3) Notably, mortality also calculated for original Gler et al. patients – 7.1% if assigned to delamanid vs 9.9% if assigned to placebo.	Observational study of initially randomized patients treated for 2 months, many of whom then moved on to an open-label treatment trial of delamanid for 6 months, with a gap in between. Variable time period between initial 2 months of delamanid and subsequent 6 months, with background standard of care regimen in between.

d. **Evidence quality:** Poor overall. 1 phase 2 RCT whose endpoints were limited to culture conversion and safety makers (Gler et al.). Other RCT (von Groote-Bidlingmaier et al.) failed to show an impact on "favourable" outcomes (cure or completion of therapy) vs "unfavourable outcomes" (death or treatment failure). Impact on treatment outcomes and survival stems from observational data, which is associated a significant risk of bias. Of note, since delamanid was added to background therapy, rather than replacing individual drugs, true effect size may be underestimated.

7. **Alternative agents:** There are several MDR regimens that do not include delamanid. WHO recommendations state that delamanid "may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens, but offers several other options for non-delamanid-containing regimens".

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [x] Uncertain: [ ]	No RCT-level evidence for improvement in mortality or cure rates.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [ ] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [x]	Lack of sufficiently good evidence to permit a firm assessment.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [x] No: [ ] List the members of the group. Moxifloxacin, clofazimine, pyrazinamide, ethambutol, ethionamide, amikacin, kanamycin, high-dose INH, ethambutol (***note that routine use of high dose INH is not supported).*** List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: It is possible to treat MDR TB without delamanid. Since 4-5 active drugs are conventionally used to treat TB, there will be many cases where alternative drugs could be used, and some of these regimens have a strong evidence base. However, many of the therapeutic alternatives may offer only marginal efficacy, and/or carry significant toxicities and/or mortality risks. In addition, in some cases, there may be no alternative drug available, depending on the individual patients' resistance patterns, comorbidities and/or side-effects, and the need to provide ~4 active drugs simultaneously.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [ ] No: [ ] Uncertain: [X]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [x]	Cost of medicines/24 week regimen: **Medicine** | **Cost(ZAR)*** Delamanid 100 mg tablets, 12 hrly x24 wks | 1409.57 *Contract circular HP01-2019TB **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes: [X] No: [ ] Uncertain: [ ]	Inequitable access to this agent, with no proven benefit.
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: [ ] No: [ ] Uncertain: [X]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☒	☐	☐	☐

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends that delaminid not be included in the Adult Hospital Level EML (that enables routine access at all secondary level facilities). The medicine is recommended for use at designated MDR-TB facilities where appropiate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees.
It is acknowledged that the short-course DR-TB regimen is a conditional WHO recommendation and is currently administered nationally under operational research conditions.

Rationale: In the context of alternative regimens available to treat MDR-TB, delamanid is an expensive agent with no apparent reduction in mortality (either TB-attributable or overall). Furthermore, in the phase III RCT there was no treatment statistically significant difference in sputum culture conversion rates at 2 or 6 months. The need for individualised management of DR-TB requires particluar consideration.
Level of Evidence: III RCTs (phase I and II); **observational studies**

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X		

VEN status:

Vital	Essential	Necessary

NEMLC MEETING OF 5 DECEMBER 2019:
NEMLC acknowledged the evidence review done by the Adult Hospital Level Committee; but recommended that delamanid be included on the national EML with a condition – "*all MDR-TB cases should be discussed with a designated specialist centre; and MDR-TB medicines to be accessed from these designated centre(s)".*
Rationale: Designated MDR-TB facilities are available at all levels of care - where appropiate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees.

Monitoring and evaluation considerations: n/a

Research priorities
RCT-level data showing significant differences in cure rates and/or mortality rates is needed.

References

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