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

MEDICINE REVIEW:

1. Executive Summary

Date: 1 August 2019
Medicine (INN): Linezolid, oral
Medicine (ATC): J01XX08
Indication (ICD10 code): Multi Drug-Resistant tuberculosis [A15-A19 + (U50.00-01)]
Patient population: Adults with rifampicin-monoresistant or multidrug-resistant tuberculosis
Prevalence of condition: 2.8% of new TB cases are multidrug-resistant in South Africa
Level of Care: Secondary level of care
Prescriber Level: Medical officer
Current standard of Care: 5 drug MDR TB regimen, with substantial toxicities.
Efficacy estimates: (preferably NNT): In Cochrane meta-analysis, NNT = 34 to prevent 1 death (note: high degree of uncertainty however)[1]
Motivator/reviewer name(s): Dr. J. Nel; Dr R de Waal
PTC affiliation: n/a

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

Primary reviewer: Dr Jeremy Nel
Secondary reviewer: Dr Renee de Waal

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)

Dr R de Waal:

- *Affiliation:* University of Cape Town; NEMLC Committee member
- *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.[2] In many such cases, the patient's TB strain may be additionally resistant to one or more of the second-line medicines conventionally used to treat MDR TB. Treatment success rates with the current standard of are regimens are suboptimal, owing to several of the constituent medicines having only marginal efficacy and/or poor side-effect profiles. Only ~22% of patients with rifampicin-resistant TB successfully complete treatment in South Africa.[3] Thus, there is a substantial need for novel drugs that have better efficacy and/or improved safety. Linezolid is one of the medicines recommended to be either add to existing regimens for drug-resistant TB, or replace one or more of the existing medicines in these treatment regimens. It is one of the recommended drugs in the World Health Organization's MDR TB guidelines.

5. Purpose/Objective i.e. PICO

-P: adult patients with rifampicin-resistant tuberculosis
-I: use of linezolid as part of a multi-drug treatment regimen
-C: standard of care multi-drug treatment regimen

-O: efficacy: culture conversion, treatment success rate, mortality rate; tolerability: grade 3 and 4 adverse events, mortality rate

6. **Methods:**
   a. **Data sources**: PubMed, Cochrane**.** Trials included were limited to randomized control trials, systematic reviews and meta-analyses.
   b. **Search strategy**
      PubMed: (("linezolid"[MeSH Terms] OR "linezolid"[All Fields]) AND ("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields])) AND (Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb])
   c. **Excluded studies:**

PMID	***Type of study***	***Reason for exclusion***
14973154	*Clinical trial*	*Murine study, no humans enrolled*
17519090	*Systematic review*	*Included patients with nontuberculous mycobacterial infections*
18787216	*Clinical trial*	*Short-term bactericidal activity study, given as monotherapy.*
20629533	*Clinical trial*	*Pharmacokinetics study, healthy volunteers.*
21078950	*Clinical trial*	*Short-term bactericidal activity study, healthy volunteers.*
22423128	*Case report*	*Single case report*
23075177	*Clinical trial*	*Extensively drug-resistant (XDR) TB only, not MDR TB*
23131255	*Report*	*Description of challenges faced during a clinical trial of linezolid in MDR patients.*
24732289	*Clinical trial*	*Trial was of a different compound, not linezolid*
26870788	*Clinical trial*	*Pharmacokinetics study, XDR TB only.*
28193240	*Study protocol*	*Study protocol*
28739794	*Clinical trial*	*Trial was of a different compound, not linezolid*
29120971	*Systematic review*	*Systematic review of salivary vs blood concentrations of TB drugs. Not relevant to PICO analysis.*
30496467	*Meta-analysis*	*Pharmacokinetics/pharmacodynamics meta-analysis of dosing regimens. Not relevant to PICO analysis.*
28049171	*Meta-analysis*	*Contained too few patients on linezolid to include this drug in the analyses*

d. Evidence synthesis

2 RCTs in XDR patients. For MDR patients, only systematic reviews/meta-analyses of observational data could be sourced.
(Note: Study cohorts generally included both XDR and MDR patients; thus evidence table below reviews the same).

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
A. Randomised control trials							
Lee M et al., 2012.[4]	RCT	41	Pulmonary XDR and hadn't responded to previous regimens	Linezolid immediately vs 2 months later. After sputum culture conversion or at 4 months (whichever sooner), patients randomized again to 300 vs 600mg for 18 months.	Time to sputum culture conversion.	Efficacy: at 4 months, 15/21 (79%) in immediate group vs 7/20 (35%) in delayed group. Safety: 82% of patients had clinically significant adverse events that were possibly or probably related to linezolid.	Complex trial design (2 randomisation episodes, variable doses, variable start times) – difficult to generalize from. Low number of patients enrolled. HIV patients excluded.
Tang S et al 2015.[5]	RCT	65	Pulmonary XDR	Placebo (each arm received background XDR regiment also)	Sputum culture conversion	Sputum culture conversion 78.8% (linezolid) vs 37.6% (placebo) – no CI given, but p <0.001. Treatment success in 69.7% (linezolid) vs 34.4% (placebo) – p=0.004.	Small numbers. Linezolid given at 1200mg daily for 4-6 weeks, then 300-600mg daily thereafter until two consecutive negative sputum culture results (i.e. variable durations). HIV patients excluded. Patients unable to purchase linezolid were excluded. No long term follow up.
B. Systematic reviews and meta-analysis							
Cox H, Ford N, 2012[6]	Systematic review	148 (11 studies)	Patients with MDR or XDR TB	None	Treatment success (variably defined), culture conversion. Adverse events.	Efficacy: Treatment success in 68% (95% CI 58-79%). Culture conversion in 98% (95-100). Safety: Adverse events in 31-79%. Peripheral neuropathy in 36% and bone marrow suppression in 28%. Linezolid stopped due to AEs in 29% for	No control group. Data all observational. Included XDR patients (28%) along with MDR. Very heterogeneous population – many different previous regimens/durations, different doses (300-1200 mg daily), different linezolid durations (1

						≤600mg daily, vs 61% for >600 mg daily.	week-48 months). Poor reporting of study details. Treatment success variably defined. Significant toxicities with linezolid, but variable doses/durations used.
Sotgui G et al., 2012[7]	Systematic review and meta-analysis	121 (12 studies)	Patients with MDR or XDR TB	None	Culture conversion, treatment success (not defined)	Efficacy: culture conversion in 94%, 82% treatment success. Safety: Adverse events from LZD in 59%. Anaemia in 38%, peripheral neuropathy in 47%, optic neuritis in 13%, thrombocytopenia in 11%. Fewer AEs with ≤600mg daily (anaemia in 22%, thrombocytopenia in 10%, optic neuritis 9.8%).	No control group. Data all observational. MDR and XDR patients both included. Only 8.7% HIV positive.
Chang KC et al., 2013[8]	Systematic review and meta-analysis	174 (20 studies)	Pulmonary XDR TB or fluoroquinolone-resistant MDR TB.	Use of linezolid vs non-use of linezolid as part of multidrug regimen	Favourable outcome (defn: sputum culture conversion, cure, or treatment completion in the absence of death, default, treatment failure, or relapse.)	Linezolid use associated with favourable outcome by robust poisson regression model (RR 1.57, CI 1.110-2.24) and random-effects meta-analysis (RR 1.55, CI 1.10-2.21).	Patient population not truly representative of MDR patients in general. Observational data.
Zhang X et al. 2015[9]	Systematic review and meta-analysis	367 (15 studies)	MDR and XDR TB.	None	Favourable outcome as per WHO definitions	Efficacy: Favourable outcome in 83% (75-90%). Death in 9.6%, treatment failure in 10.9%. Safety: Major adverse events in 35% (22-47%). Peripheral neuropathy 31%, anaemia 25%, optic neuritis 8%, thrombocytopenia 7.6%, leukopenia 7.3%. Lower haematological and peripheral nervous system side effects with ≤600mg daily, but still substantial.	XDR patients included as well. Significant heterogeneity in studies included.

Agyeman AA, Ofori-Asenso R. 2016[10]	Systematic review and meta-analysis	507 (23 studies)	MDR and XDR TB.	None.	Treatment success (most but not all studies similar to WHO definitions), culture conversion rate, adverse events.	Efficacy: Sputum culture conversion in 88% (CI 84-92%). 77% treatment success (71-83%). Safety: Major adverse events leading to permanent discontinuation in 16% (10-23%). Myelosuppression in 33% (23-44), neuropathy in 30% (21-40%). Less myelosuppression with ≤600mg daily.	XDR patients included as well. Significant heterogeneity in studies. Only 3% of patients were HIV positive.
Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment-2017. 2018[11]	Individual patient data meta-analysis	12030 (50 studies)	MDR and XDR TB.	Linezolid vs non-linezolid regimens	Treatment success (defn: cure or completion) vs failure or relapse. Death (all-cause) vs success or failure or relapse.	OR for success 3.4 (2.6-4.5). OR for death 0.3 (0.2-0.3) in propensity score matched multivariate regression.	Observational studies predominantly, heterogenous regimens and locations. Pregnancy and extrapulmonary-only subgroups could not be analysed due to limited numbers.
Singh B, et al. 2019[1]	Systematic review	104 from two RCTs, and 1678 from 14 non-randomised cohort studies.	MDR and XDR pulmonary tuberculosis	Linezolid vs no-linezolid as part of multidrug regimens	Cure, treatment completion, sputum culture conversion at 24 months, adverse events, death	Efficacy: Cure RR 2.36 (1.13-4.90), treatment completion RR 1.45 (0.45-4.68), sputum culture conversion 2.1 (1.3-3.4). Safety: Adverse events unable to be calculated (lack of reporting on follow-up duration). Death RR 0.65 (0.12-3.62)	All findings reported with "very low" degree of certainty due to risk of bias, imprecision and indirectness. MDR and XDR patients included.

a. **Evidence quality:** Low. No RCTs for MDR (only XDR). Most trials included both MDR and XDR and many did not distinguish outcomes between these two conditions. RCTs enrolled low numbers of patients. Overall, high risk of bias, and considerable heterogeneity in trials with regards to linezolid dosing, duration and background regimen. HIV patients excluded from bulk of trials.

7. **Alternative agents:** There are several MDR regimens that do not include linezolid. However, whether most of the alternative agents are any more efficacious is not known.

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: [ ]	See evidence quality above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [ ] Harms outweigh benefits: [x] Benefits = harms or Uncertain: [ ]	See evidence synthesis table, above.
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, bedaquiline, delamanid ***(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 linezolid. Since 4-5 active medicines are conventionally used to treat TB, there will be many cases where alternative medicines 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 medicine available, depending on the individual patients' resistance patterns, comorbidities and/or side-effects, and the need to provide ~4 active medicines 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]	It is noted that the NDoH TB DR Programme recommends linezolid as part of the DR-TB regimen in the NDoH Interim Guidelines.
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [x]	Cost of medicines/ treatment course: **Medicine** | **Cost (ZAR)*** Linezolid 600mg daily x8 weeks (56 tablets) | R3049.87 ***** Contract circular HP02-2019AI; Linezolid 600 mg 10 tablets: R544.62 *Note: 600mg daily likely equivalent efficacy to 1,200mg daily in TB, but with fewer side-effects.*[12] **Additional resources:** N/A
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [ ] Uncertain: [X]	The skills to detect serious adverse events may not be available at all levels of care i.e.: • Optic neuritis/neuropathy • Myelosuppresion • Peripheraphal neuropathy
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
	☐	☐	☐	X	☐

Recommendation: Based on the evidence review, above, the Adult Hospital Level Committee recommends that linezolid 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: Low quality of evidence for use of linezolid in MDR TB; noting the lack of efficacy and serious adverse events (i.e. optic neuritis/neuropathy, peripheral neuropathy and mylesuppresion). It is acknowledged that the results of STREAM II will be available in due course, as this RCT is currently still enroling study participants, that will further inform decision-making. The need for individualised management of DR-TB requires particluar consideration.
Level of Evidence: III Systemic review and meta-analyses of observational studies, 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 linezolid 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: Need RCT-level data showing benefit in MDR regimens.

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