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): Bedaquiline, oral
Medicine (ATC): J04AK05
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: Secondary level of care
Prescriber Level: Medical Officer
Current standard of Care: ≥5 drug MDR TB regimen, with substantial toxicities.
Efficacy estimates: (preferably NNT) NNT to obtain sustained culture conversion at 120 weeks = 6 (Diacon et al. 2014).[2]
Motivator/reviewer name(s): Dr J. Nel; Prof K Cohen
PTC affiliation: Prof K Cohen – WC Provincial PTC

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

Primary reviewer: Dr Jeremy Nel
Secondary reviewer: Prof Karen Cohen

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)

Prof K Cohen:

- *Affiliation:* University of Cape Town; National Essential Medicines List Committee
- *Conflict of interests:* None declared. ?Western Cape provincial HIV and TB programmatic pharmacovigilance retrospective analysis of ADRs associated with bedaquiline (Jones et al, 2019)

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.[3] Thus, there is a substantial need for novel drugs that have better efficacy and/or improved safety. Bedaquiline 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 bedaquiline 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.
   b. **Search strategy**
   PubMed: (("bedaquiline"[Supplementary Concept] OR "bedaquiline"[All Fields]) AND ("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR ("tuberculosis"[All Fields] AND "tb"[All Fields]) OR "tuberculosis tb"[All Fields])) AND (systematic[sb] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp])

   PubMed was searched for randomized control trials, meta-analyses, and systematic reviews using the search terms "bedaquiline", "tuberculosis", and "TB". We included systematic reviews and meta-analyses of observational studies. For efficacy analyses, only trials with a comparator were included. For safety analyses, no comparator was required.

   The Cochrane reviews were searched for reviews containing the terms "bedaquiline", "tuberculosis", and "TB".

   There were no applicable results found in the Cochrane reviews.
   In PubMed, 19 studies were identified:

   - 1 was rejected because it was a study in mice, not humans.
   - 7 were rejected because they were early bactericidal activity studies and/or pharmacokinetic studies of bedaquiline with no endpoints relevant to the PICO analysis.
   - 1 was rejected because it was an *in vitro* study of two competing measures of early bactericidal activity, and thus had no outcomes relevant to the PICO analysis.
   - 1 was rejected because it was purely a comparison between 8 and 24 week culture conversion as surrogate endpoint in bedaquiline trials.
   - 2 were rejected because they assessed the combined use of bedaquiline and delaminid, but did not assess the use of bedaquiline (alone) in conjunction to standard-of-care regimens.
   - 1 was rejected since it was limited to children.
   - 1 systematic review was not included to minimise duplication of reviewing data/evidence - because the only two trials which it included are separately analysed below, and because of queries that have subsequently been raised about its methodology PMID: 27756966 (i.e. fixed-effect model rather than random-effect model was used; placebo group reported less mortality than bedaquiline group for MDR-TB – however, confounding and selection bias was present and the causality of mortality to bedaquiline could not be determined).1 was rejected because it reported preliminary findings that were later superseded by a later publication that was included.

In addition, one relevant evidence alert was received regarding a local retrospective analysis of adverse drug reactions associated with bedaquiline (Jones et al, 2019[4]) that describes experience of ADRs in the South African setting.

c. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
A: Randomised control trials							
Diacon et al., 2012.[5]	RCT	47	Adults 18-65y with smear-positive MDR pulmonary TB.	Bedaquiline (BDQ) vs placebo for 8 weeks, both given in addition to standard durations of background treatment of kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone. Background regimen continued after BDQ stopped Modifications to background regimen permitted as needed.	Culture negativity at 24 weeks, adverse events	Culture negativity at 24 weeks HR 2.25 (1.08-4.71, p=0.031) favouring BDQ. More nausea (24% vs 0%) in BDQ group, but no other statistically significant differences in adverse events. 1 myocardial infarction in BDQ group deemed unrelated to study medication. Greater increase in QTcF seen in BDQ group, but none >500 ms (no further details given)	BDQ given for 8 weeks, not 24 as is now standard. Single country (SA). Important exclusions: neurological or severe extrapulmonary TB, CD4 <300, ART or antifungal treatment within past 90 days, quinolone or aminoglycoside resistance, pregnancy, etc. Discontinuations during 1st 24 weeks counted as culture positives, irrespective of microbiological status; 13 discontinuations in placebo group vs 10 in BDQ group, so intrinisically favoured BDQ.
Diacon et al., 2014.[2]	RCT	160	Adults 18-65 with smear-positive	Bedaquiline (BDQ) for 24 weeks vs placebo, both in combination with	Time to culture conversion. Secondary end-points: rates of	More patients in BDQ group achieved culture negativity at 24	High discontinuation rate (38%, though evenly split between groups). Reason for

			pulmonary MDR TB	standard background regimen in relevant country.	culture conversion at 24 & 120 weeks.	(79 vs 58%, p=0.008) and 120 weeks (62 vs 44%, p=0.04). On the basis of WHO cure definition, more patients in BDQ group were cured (58 vs 32%, p=0.003). Grade 3/4 adverse events were not statistically significantly different (43 vs 36%). Death occurred in 13 vs 2% though (p=0.02). QTcF prolongation greater in BDQ group, but only >500 ms in 1 patient.	increased mortality unclear, but no clear link to BDQ in detailed patient profiles of the deaths (supplementary appendix table S5). Important exclusions to the trial: HIV with CD4 <300, complicated or severe extrapulmonary or neurological TB, pregnancy, QTcF >450ms, etc.
B: Systematic reviews and meta-analyses							
Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017[6]	Individual patient data meta-analysis	12030 patients from 25 countries in 50 studies	MDR TB cases. Studies reporting original results of at least 25 adults.	Multivariate regression comparing treatment regimens, matched for propensity score	Treatment success (defn: cure or completion) and mortality	Significantly fewer deaths: adjusted aOR 0.4 (0.3-0.5), and more treatment successes: aOR 2.0 (1.4-2.9) with BDQ use. Similar results	Observational design, heterogenous regimens and locations. Pregnancy and extra-pulmonary only subgroups could not be analysed due to limited numbers.

						for XDR TB cases.	
Mbuagbaw et al, 2019 [7]	Individual patient data meta-analysis	537 patients from 5 cohort studies	Adults with DR-TB (either MDR-TB or XDR-TB). Mean age 36.4 years (SD 11.8); mostly men (63.7%); 25.7% were HIV positive;99.7% had pulmonary TB & 73.9% had lung cavities.	BDQ-containing DR-TB regimens, with baseline regimens determined by local treatment guidelines, drug susceptibility results, or both.	Cure, treatment completion, treatment success (the sum of cure and treatment completion), loss to follow-up, and death.	Culture conversion rate at 6 mo: 78.0% (73.5%–81.9%; I^2 = 46%); Cure, 60.1% (50.2%–69.2%; I^2 = 66%); Treatment success, 65.8% (59.9%–71.3%; I^2 = 38%); Death, 11.7% (7.0%–19.1%; I^2 = 71%); failure, 5.1% (1.6%–14.8%; I^2 = 73%); Loss to follow-up, 14.8% (11.6%–18.7%; I^2 = 7%). Treatment success less likely in patients with lung cavitations (aOR 0.38, 0.21–0.68; p = 0.001) and in HIV infected (aOR 0.35, 0.12–0.99; p = 0.05). Lung cavitations associated with	Observational study with heterogeneity across cohorts.

						death (aOR 5.31, 1.25–22.52; p = 0.023)	
Pontali et al. 2017.[8]	Systematic review	23 studies, 1303 patients	Patients who received BDQ. Studies required clear description of safety profile and cardiac adverse events.	N/A	BDQ discontinuation rates and cardiac safety parameters	3.5% stopped BDQ due to tolerability or safety concerns. 0.6% stopped due to prolonged QTc. QTc >500 ms occurred in 3.2%.	Many potentially relevant cohort studies did not provide sufficient detail on QTc and/or cardiac adverse events. Discontinuation rate for prolonged QTc only 0.6% , but 3.2% had QTc > 500 ms.

d. **Evidence quality:** Low quality overall. Two phase 2 RCTs, one with 47 patients, and the other with 160 patients. Important subgroups excluded from the RCTs including HIV positive patients with CD4 <300, extrapulmonary/neurological TB, and pregnant patients. The only RCT assessing mortality showed an increase in mortality in the BDQ arm, although there was no clear causal link to BDQ identified. Individual patient data meta-analyses included large numbers of patients, but are limited by observational design, with a strong risk of bias.

7. **Alternative agents:** It is possible to treat MDR TB without bedaquiline. By way of example, the STREAM1 trial compared two non-BDQ-containing regimens to treat rifampicin-resistant TB pulmonary TB cases, the shorter of two regimens consisting of moxifloxacin, clofazimine, ethambutol, pyrazinamide, kanamycin, isoniazid and prothionamide together.[9] Since 4-5 active drugs are conventionally used to treat TB, there will be many cases where alternative drugs could be used. However, many of the 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.

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: [ ] Uncertain: [X]	Two RCTs, a large-scale individual patient data meta-analysis, and a large systematic review provide good evidence for increased sputum culture conversion in BDQ-regimens. Evidence on mortality is mixed however, with one RCT showing increased mortality, but decreased mortality seen from observational studies. Good evidence re: safety, though many patients at risk of prolonged QTc excluded.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [ ] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [x]	In the one RCT to measure mortality, mortality was significantly higher in the BDQ group. However, close attention to the individual patient histories revealed no obvious mechanism for this, and the meta-analysis of observational data revealed a mortality benefit in giving BDQ.
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 bedaquiline. 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. References: See evidence synthesis, above.

<table>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [x] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [ ] Uncertain [x]</td><td>Cost of medicines/24 week regimen:
<table><tr><th>Medicine</th><th>Cost (ZAR)**</th></tr><tr><td>Bedaquiline 100 mg (188 tabs)*</td><td>5400.00</td></tr></table>* 400 daily x 2wks, then 200mg thrice weekly x 22wk
**Contract circular RT78-2017 (188 tabs = R5400; unit cost = R28.723)
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [x] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

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, the Adult Hospital Level Committee recommends that bedaquiline (BDQ) 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: The evidence base for BDQ in MDR and XDR tuberculosis treatment regimens is limited; and is currently insufficient in terms of mortality outcomes. Additional RCT data on mortality would further inform decision-making. Phase 3 RCTs, including the STREAM2 trial are currently underway, that will permit firmer recommendations to be made in this regard. There is also currently insufficient high-quality evidence to recommend BDQ in pregnant women, HIV patients with CD4 <300, and severe extra-pulmonary or neurological disease. Outcomes with BDQ may be worse in important subgroups such as those with cavitatory disease, and BDQ requires periodic ECG monitoring due to its propensity to increase the QTc interval. The need for individualised management of DR-TB requires particluar consideration.

Level of Evidence: III Disease oriented RCTs, Observational studies

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X		

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC acknowledged the evidence review done by the Adult Hospital Level Committee; but recommended that bedaquiline 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

More RCT data is needed on mortality rates.

More RCT data is needed for important subgroups hitherto excluded (as above).

References

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