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

MEDICINE REVIEW:

1. Executive Summary

Date: 10/09/19
Medicine (INN): Clofazimine
Medicine (ATC): J04BA01
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: Hospital level
Prescriber Level: Medical Officer
Current standard of Care: ≥5 drug MDR TB regimen.
Efficacy estimates: (preferably NNT) NNT = 6 (Duan et al.) to achieve 1 favourable outcome (cure or completion).
Motivator/reviewer name(s): Dr J Nel, Dr H Dawood
PTC affiliation: Dr H Dawood – KZN Provincial PTC

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

Primary reviewer: Dr Jeremy Nel
Secondary reviewer: Dr H Dawood

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:* Consulting work for Mylan and AbbVie.

Dr H Dawood:

- *Affiliation:* Greys hospital, KZN Department of health; Caprisa, UKZN; Chair of the Adult Hospital Level Committee (2017-2020); Member of the National Essential Medicines List Committee.
- *Conflict of interests: MSD*: ECMID 2018 - Conference attendance; ACTA study - DSMB member (crypto meningitis); Adcock Ingram - HIV discussion with general practitioners.

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 prevalence of the closely-related rifampicin-monoresistant and extensively drug resistant (XDR) strains were 3.4% and 4.9%.[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 and tolerance and/or reduced treatment duration. Clofazimine is a novel anti-tuberculous agent that has been recommended by the World Health Organization as part of a new multi-drug regimen to treat MDR tuberculosis.

5. Purpose/Objective i.e. PICO question

-P: adult patients with rifampicin-resistant tuberculosis
-I: use of clofazimine 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, World Health Organization consolidated guidelines on drug-resistant tuberculosis.

b. Search strategy

PubMed: (("clofazimine"[MeSH Terms] OR "clofazimine"[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 Clinical Trial[ptyp] OR Meta-Analysis[ptyp])

PubMed was searched for randomized control trials, systematic reviews and meta-analyses relating to the terms “clofazimine” and “tuberculosis” or “TB”. Only trials/reviews/meta-analyses with a control group were considered.
The World Health Organization’s consolidated guidelines on drug-resistant tuberculosis (2019) were also consulted for their evidence summaries relating to clofazimine.
The Cochrane library was searched for reviews on clofazimine in MDR TB.

c. Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
O’Brien et al. 1990	RCT	Study of rifabutin in pulmonary *Mycobacterium avium* (MAC) infection.
Thomas A, et al. 1990	RCT	Study of treatment for leprosy.
Dautzenberg B, et al. 1991	Observational	Study of patients with nontuberculous mycobacterial infections
Thomas A, et al. 1990	RCT	Study of treatment for leprosy.
Roussel G, et al. 1998	Clinical trial	Study of treatment regimen in patients with MAC.
Nix DE, et al. 2004.	PK trial	PK trial in healthy volunteers.
Van Deun et al. 2004	Observational trial	No control group. Data included in other meta-analyses and systematic reviews.
Feller M, et al. 2010	Systematic review and meta-analysis	Assessment of long-term antibiotics for Crohn’s disease.
Gopal et al. 2013	Systematic review	No control group in any of the included studies.
Dey et al. 2013	Systematic review and meta-analysis	No control group in any of the included studies.
Hwang TJ et al. 2014	Meta-analysis	No control group.
Nunn AJ et al. 2014	Trial description	STREAM trial design description (no results)
Diacon AH et al. 2015	RCT	Study of early bactericidal activity of various drug combinations. No outcomes relevant to PICO analysis.
Ahmad Khan F et al. 2017	Meta-analysis	No outcomes relevant to PICO reported for CFZ.

d. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Chang KC et al. 2013[2]	Systematic review and meta-analysis	194, from 20 studies	MDR TB	Clofazimine (n=65) vs non-clofazimine regimen	Favourable outcome (cure or completion)	Univariate analysis: RR of 0.83 (p=0.04) with use of clofazimine (i.e. associated with worse outcome). Robust Poisson regression model (RR = 1.01, 95% CI 0.8-1.26) and random-effects meta-analysis (RR = 0.99 (0.76-1.31) showed no significant benefit to using clofazimine (but unlike univariate analysis, no significant harm).	Only 3 patients had HIV infection. Considerable heterogeneity between studies. Data observational.
Tang S, et al. 2014[3]	RCT	105	Sputum culture positive (i.e. pulmonary) MDR from 6 major TB hospitals in China.	Each arm received individualized regimens consisting of at least 5 drugs, and CFZ arm had CFZ added in addition.	Sputum culture conversion (primary outcome), treatment success (cure or completion), adverse events.	Sputum culture conversion earlier with CFZ (p=0.042). Treatment success in 73.6% of CFZ group, vs 53.8% of controls (p=0.04). Death rates equivalent (p=1). Adverse events: discolouration of skin in 94% vs 0%, ichthyosis in 47% vs 0%.	Short-term follow up only. HIV patients excluded. No placebo. Participation rate not stated (risk of bias).
Fox GJ, et al. 2017[4]	Individual patient data meta-analysis	9282 patients from 31 studies	Pulmonary MDR-TB ,+/- extra-pulmonary TB, +/- resistance to other antibiotics.	CFZ-containing regimens (n=806) vs non-CFZ-containing regimens, calculated using a random effects meta-analysis.	Treatment success vs combined outcome of failure, relapse, or death.	CFZ treatment effect varied by analytic method used: unadjusted vs, multivariate logistic regression, vs propensity score matching, etc. Clofazimine either showed no benefit, or an association with reduced treatment success depending on the method chosen. E.g. OR 0.7 (95% CI 0.3-1.4) of treatment success compared to death, failure, relapse or loss to follow-up.	Mostly observational data (risk of bias).
Duan H et al. 2019[5]	RCT	140	Adults with smear-positive pulmonary MDR TB in China. XDR excluded.	Background MDR regimen with or without CFZ for full 24-month treatment period.	Treatment success (primary outcome, cure or treatment completion), death, adverse events.	Favourable outcome in 65.1% vs 47.3% (p=0.034, RR 0.66, 95% CI 0.24-0.95). Adverse events: statistically significantly more skin discolouration (12% vs 0%) and hepatitis (12.1% vs 2.7%).	Unblinded (no placebo). Pregnancy was an exclusion criterion. Treatment success determined at the end of treatment course (i.e. relatively short follow-up, albeit still 24 months).
Wang et al. 2018[6]	RCT	49	Adults with pulmonary XDR TB in China.	Background 6 drug regimen, with or without CFZ.	Treatment success (cure or completion)	CFZ arm had 34.6% treatment success (31.8% cure and 4.5% completed) vs 44.4% treatment success for non-CFZ arm (22.2% cure and 22.2% completion). Skin discolouration (22.7% vs 0%) and hepatic damage (31.8% vs 11.1%) were statistically more common in the CFZ group.	Small numbers limited power of study. Pregnant, breastfeeding, and HIV patients excluded. No placebo given.

Ahmad N et al. 2018[7]	Individual patient data meta-analysis	12,030, from 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 (definition: cure or completion) and mortality	Treatment success positive correlated with clofazimine use: aOR 1.5 (95% CI 0.9-2.6) and reduced odds of death: aOR 0.4 (0.2-0.6)	Observational data, heterogenous regimens and locations. Pregnancy and extra-pulmonary-only subgroups could not be analysed due to limited numbers.
World Health Organization. 2018[8]	Individual patient data meta-analysis	Subset of Ahmad N et al. meta-analysis for which AEs resulting in permanent discontinuation of a TB medication (27 studies) or classified as grade 3-5 (3 studies) were reported.	MDR TB cases. Studies reporting original results of at least 25 adults.	Multivariate regression comparing treatment regimens, matched for propensity score	Absolute risk of permanent discontinuation of CFZ, or grade 3-5 AE related to CFZ.	3.6% (95% CI 1.5-5.8)	3.6% compares favourably with other individual drugs assessed – see table 2.3 from WHO report reproduced below.

Table 2.3. Serious adverse events (SAEs) in patients on longer MDR-TB regimens*

Medicine	Absolute risk of SAE	
	Median (%)	95% credible interval
Bedaquiline	2.4	[0.7, 7.6]
Moxifloxacin	2.9	[1.4, 5.6]
Amoxicillin–clavulanic acid	3.0	[1.5, 5.8]
Clofazimine	3.6	[1.3, 8.6]
Ethambutol	4.0	[2.4, 6.8]
Levofloxacin	4.1	[1.9, 8.8]
Streptomycin	4.5	[2.3, 8.8]
Cycloserine/terizidone	7.8	[5.8, 10.9]
Capreomycin	8.4	[5.7, 12.2]
Pyrazinamide	8.8	[5.6, 13.2]
Ethionamide/prothionamide	9.5	[6.5, 14.5]
Amikacin	10.3	[6.6, 17.0]
Kanamycin	10.8	[7.2, 16.1]
p-aminosalicylic acid	14.3	[10.1, 20.7]
Thioacetazone	14.6	[4.9, 37.6]
Linezolid	17.2	[10.1, 27.0]

* From an "arm-based network" meta-analysis of a patient subset from the 2016 IPD for which AEs resulting in permanent discontinuation of a TB medicine (27 studies) or classified as Grade 3–5 (3 studies) were reported. There were insufficient records on delamanid, imipenem–cilastatin and meropenem to estimate risks. Agents that are not in Groups A, B or C are italicized.

Source: WHO consolidated guidelines on drug-resistant tuberculosis treatment[8]

e. **Evidence quality:** Moderate: 2 RCTs MDR TB both show significant benefit, albeit in unblinded trials. Also multiple systemic reviews and meta-analyses, though made up predominantly of observational data with large amounts of heterogeneity and risk of bias, and mixed results. 1 RCT for XDR showed no benefit of CFZ, but underpowered.

7. **Alternative agents:** Multiple drugs can be incorporated into MDR and XDR regimens. As per WHO guidelines, these include, bedaquiline, fluoroquinolones, ethambutol, amikacin, streptomycin, pyrazinamide, high-dose INH, ethionamide, linezolid, etc.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [x] Not confident [ ] Uncertain [ ]	Based on the 2 RCTs *see above) demonstrating efficacy for CFZ-containing regimens for MDR-TB: moderately confident For XDR TB, uncertain.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	See table above extracted from WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment. Clofazimine appears to be among the safer medicines available to treat MDR TB.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [x] No [ ] List the members of the group. bedaquiline, fluoroquinolones, ethambutol, amikacin, streptomycin, pyrazinamide, high-dose INH, ethionamide, linezolid ***(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 clofazimine. 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 therapeutic alternatives may offer only marginal efficacy, and/or carry significant toxicities and/or mortality risks. Clofazimine appears to be an important part of MDR treatment regimens, with better outcomes seen in RCT trials when it was used. In addition, in some cases, there may be no alternative drug available, depending on the individual patients' resistance patterns, and comorbidities.
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]	

<table>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [X]</td><td>Cost of medicines/treatment course:
<table><tr><th>Medicine</th><th>Cost (ZAR)*</th></tr><tr><td>Clofazimine 100mg daily x18-20 months (long regimen)</td><td>4243.68 to 4715.20</td></tr><tr><td>Clofazimine 100mg daily x9-11 months (short regimen)</td><td>2121.84 to 2593.36</td></tr></table>* Contract circular HP01-2019TB: Clofazimine 100 mg tablets (100) = R842.00
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [x] No [ ] Uncertain [ ]</td><td>Not SAHPRA registered; access is variable</td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [ ] No [ ] Uncertain [x]</td><td>Not SAHPRA registered; access is variable</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 clofazimine not be included in the Adult Hospital Level EML that enables routine access of this medicine at all secondary level facilities. The medicine is recommended for use at designated MDR-TB facilities where appropriate 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**.** Clofazimine requires SAPHRA registration.
Rationale: There is evidence for clofazamine's efficacy as part of a multi-drug combination regimen for MDR TB. The severe adverse event rate is better than most of the current MDR-TB drugs. The need for individualised management of DR-TB requires particluar consideration.
Level of Evidence: I RCT

Review indicator(s): **SAHPRA registration status, price**

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: RCT data for XDR TB is needed.

References:

1. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779-87.
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3. Tang S, Yao L, Hao X, Liu Y, Zeng L, Liu G, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. Clin Infect Dis. 2015;60(9):1361-7.
4. Fox GJ, Benedetti A, Cox H, Koh WJ, Viiklepp P, Ahuja S, et al. Group 5 drugs for multidrug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J. 2017;49(1).
5. Duan H, Chen X, Li Z, Pang Y, Jing W, Liu P, et al. Clofazimine improves clinical outcomes in multidrug-resistant tuberculosis: a randomized controlled trial. Clin Microbiol Infect. 2019;25(2):190-5.
6. Wang Q, Pang Y, Jing W, Liu Y, Wang N, Yin H, et al. Clofazimine for Treatment of Extensively Drug-Resistant Pulmonary Tuberculosis in China. Antimicrob Agents Chemother. 2018;62(4).
7. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDRTBt, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821-34.
8. World Health Organization. WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment 2019 [Available from: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/.