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

MEDICINE REVIEW

1. Executive Summary

Date: 19 October 2018
Medicine (INN): Lithium, oral
Medicine (ATC): N05AN01
Indication (ICD10 code): Bipolar Disorder, first line option for treatment and prevention of any episode (F31.0 – F31.9), where laboratory monitoring is accessible and individual patient profile is suitable
Patient population: Adults
Prevalence of condition: Worldwide prevalence 2-3%
Level of Care: Secondary level of care (District and Regional Hospital level)
Prescriber Level: Specialist / Medical Officer under specialist supervision and re-prescribing
Current standard of Care:
Mania, treatment and prevention: Risperidone, oral (acute treatment), lithium and/or valproate (maintenance)
Depression, treatment and prevention: fluoxetine + olanzapine and/or lithium and/or valproate or lamotrigine or carbamazepine
Efficacy estimates: (preferably NNT)
Maintenance treatment: prevention of any episode, NNT 4; mania/ hypomania, NNT 7; depression, NNT 16 (using RCT events as reported by Miura, 2014)
Acute mania, NNT=5 (Butler 2018)
Acute depression, no evidence of efficacy
Primary outcome:

- *Acute treatment of mania*: Response (>50% reduction in YMRS) *and* significant mean difference in change of YMRS score, both at 3 weeks
  - vs placebo (Butler et al): Response rate, NNT 5 (2 RCTs, *Bowden 2005*, n=193, Odds Ratio 3.00 (95% CI 1.265 to 5.47), *Kushner 2006* n=654, Odds Ratio 2.20 (95% CI 1.57 to 3.08)). Change in YMRS (2 RCTs, n=643), pooled result, random effects model, SMD 5.81 (95% CI 2.21 to 9.4)

- *Acute treatment of depression*: >50% reduction in symptom rating scale and significant standardized mean difference in change of depression symptoms
  - At 8 weeks (Selle, 2014, 1 RCT, n=265): Response rate: NNT 15; SMD in change of depression symptoms non-significant.
  - At 12 weeks (Butler, 2018, 1 RCT, n=283): less antipsychotic use when combined with optimized personal treatment vs optimized personal treatment alone
- *Maintenance treatment:*
  Prevention of any episode
  - vs placebo (Miura et al): Network meta-analysis, RR 0.62 (95% CI 0.53,0.72); RCT events NNT 4
  - vs valproate: not significant (Butler et al)

  Prevention of mania
  - vs placebo (Miura et al): Network meta-analysis, RR 0.58 (95% CI 0.45, 0.76); RCT events NNT 7

  Prevention of depression
  - vs placebo (Miura et al): Network meta-analysis, RR 0.58 (95% CI 0.45, 0.76); RCT events NNT 16

Motivator/reviewer name(s): Dr L. Robertson
PTC affiliation: Gauteng Provincial PTC, Sedibeng District PTC

YMRS=Young mania rating scale

2. Name of author(s)/motivator(s)
Dr Lesley Robertson

3. Author affiliation and conflict of interest details

- Dr Lesley Robertson: Affiliated to the University of the Witwatersrand, the South African Society of Psychiatrists, Adult Hospital Level Committee member (2017-2020). Conflict of interests: Dr Reddys: Annual congress attendance and accommodation, 2014 – 2019; AstraZeneca: Lunch 25 July 2017; Sanofi: Lunch 21 March 2018; Lundbeck: Lunch 29 January 2019.
  Note: Dr Lesley Robertson was recused from the final decision-making process regarding a recommendation.

4. Introduction/Background

Expert opinion argues for lithium to be used as first-line acute treatment of mania with continuation into maintenance treatment.[1] Miura et al (2014)[2] also argue for lithium as first line treatment in bipolar disorder overall. In their network meta-analysis, lithium and quetiapine are the only medicines to show efficacy in the prevention of any mood episode, mania, and depression. However, the evidence base for lithium is graded as moderate, whereas that for quetiapine is low. The authors argue that lithium is the only medicine with evidence of efficacy in non-enriched, un-biased study designs. In addition, Butler et al (2018)[3] found lithium to be the only medicine with enough evidence to recommend its use in the prevention of any mood episode in maintenance treatment.

Other arguments favouring lithium as first-line treatment in overall management of BD revolve around an associated protective effect against suicide,[4] beneficial effects on grey and white matter volume,[5, 6] and possible improvement in pro-inflammatory cytokines.[7]

5. Purpose/Objective

To review the evidence for lithium as treatment of choice in BD
- P: Patients with bipolar disorder
- **I**: Lithium
- **C**: Placebo /Alternative BD treatment
- **O**: Response rate (>50% reduction in symptoms) and mean difference in change of in acute symptoms; Time to recurrence and relapse rate in maintenance treatment

6. Methods

Search strategy:

- As described in the attached overview of BD.
  - Evidence for this review taken from Butler et al (2018),[3] Miura et al. (2014),[2] Kessing et al (2017),[8] and Smith & Cipriani (2017)[4]
- To ensure no recent studies on alternative medicines as monotherapy in maintenance treatment of bipolar disorder were missed, a second Pubmed search was conducted on 04/05/2019 using search terms “lithium, carbamazepine, lamotrigine, valproate, clozapine, olanzapine, quetiapine, risperidone, antidepressants” AND “bipolar disorder” AND “maintenance OR long-term OR relapse OR recurrence OR hospitalisation” for any papers published in English since 01/01/2017 (see Appendix III, additional searches).
  - One observational study which was not included in Kessing et al (2017) was identified: (Joas et al., 2017).[9] This study evaluated treatment of individuals with bipolar disorder in Swedish registries (N= 35 022), using a model of analysis which assessed within-individual efficacy comparing time-on and time-off the respective treatments, addressing some confounders inherent to naturalistic data. Six medicines in monotherapy were studied: lithium, valproate, carbamazepine, olanzapine, and quetiapine.
  - One review on the anti-suicidal effects of lithium by Tondo and Baldessarini (2018).[10]

Evidence synthesis:

<u>Acute treatment of mania</u>

- Vs placebo: Butler et al. (2018)[3], 2 RCTs confirm efficacy in acute mania (NNT 5), with no significant difference in harms (NNH 42).
- Vs valproate: Butler et al. (2018),[3] 1 RCT (n=270) no significant difference between lithium and valproate.

<u>Acute treatment of depression</u>

- Vs placebo: No RCT evidence of efficacy at 12 weeks (no RCTs conducted) or 8 weeks (1 RCT.
- Vs 'optimised personal treatment (without lithium)': 1 pragmatic RCT (N=283) revealed less usage of SGAs when lithium was prescribed in acute depression.

Maintenance treatment

- Vs placebo: RCT and network meta-analysis – see Table 1.
- Vs valproate: no significant difference in prevention of any mood episode, mania or depression (see Table 2 for evidence from RCTs)
- Vs other medicines: Observational study evidence – see Table 3

Table 1. Lithium vs placebo, efficacy and tolerability as reported by Miura et al (2014) and Butler et al (2018)

Mood state	Eligible RCTs	NNT	NNH	Butler et al., 2018[3] Time to recurrence	Miura et al., 2014[2] Network meta-analysis Risk ratio (95% CI)
Any mood episode	*Melia et al 1970* N=11	4	Not reported	Not included	Efficacy RR 0·62 (0·53–0·72) Tolerability RR 2·58 (1·33–5·39) Acceptability RR 0·83 (0·70–0·96)
	Cundall et al 1972 N=13	2		Not included	
	Prien et al 1973a N=44	3		Not included	
	Prien et al 1973b N=205, manic-depressive manic type	3	101	Favors Lithium p<0.001	
	Dunner et al 1976 N=40	8	Not reported	Not included	
	Kane et al 1982 N=22	2		Not included	
	Bowden et al 2000 N=372, all BD-I	13		NS	
	Bowden et al 2003 N=175, all BD-I	3	5	Log rank favors Lithium, p=0.001	
	Calabrese et al 2003 N=413, all BD-I	12	17	Log rank favors Lithium p=0.03	
	Weisler et al 2011 N=1172, all BD-I manic, mixed, or depressed	4	73	Favors Lithium HR 0.46 (95% CI 0.36, 0.59), p<0.0001	
	Events combined	**4**	**28**	-	
Mania/ hypomania	*Dunner et al 1976*	5	-	Not included	RR 0·58 (0·45–0·76)
	Fieve et al 1976 N=53	6	-	Not included	
	Kane et al 1982	7	-	Not included	
	Bowden et al 2000	68	-	NS	
	Bowden et al 2003	4	-	Log rank favors Lithium, p=0.006	
	Calabrese et al 2003	13	-	Log rank NS	
	Weisler et al 2011	6	-	Favors Lithium HR 0.37 (95% CI 0.27, 0.53), p<0.0001	
	Events combined	**7**	-	-	
Depression	*Dunner et al 1976*	-16	-	Not included	RR 0·76 (0·61–0·93)
	Fieve et al 1976	7	-	Not included	
	Kane et al 1982	3	-	Not included	
	Bowden et al 2000	16	-	NS	
	Bowden et al 2003	12	-	Log rank NS	
	Calabrese et al 2003	121	-	Log rank NS	
	Amsterdam et al 2010 N=53, all BD-II	-17	-	Log rank NS	
	Weisler et al 2011	13	-	Favors Lithium HR 0.59 (95% CI 0.42, 0.84), p<0.004	
	Events combined	**16**	-	-	

NNH=number needed to harm (withdrawal due to unspecified adverse event); NNT=number needed to treat; NS=not significant; RR=risk ratio

Table 2. Lithium vs valproate, efficacy and tolerability, as reported by Miura et al (2014)[2] and Butler et al (2018)[3]

Mood state	Eligible RCTs	NNT	NNH	Butler et al., 2018 Time to recurrence
Any mood episode	*Bowden et al 2000* N=372, all BD-I	-15	Not reported	NS
	Calabrese et al 2005 N=60, BD-I and BD-II	-16	8	Not included
	Geddes et al 2010 n=220, all BD-I manic (Balance trial)	10	55	Hazard ratio Favors Lithium HR 0.71 (0.51–1.00) p=0.047
	Events combined	**-16**	**24**	-
Mania/ hypomania	*Bowden et al 2000*	-31	-	NS
	Calabrese et al 2005	37	-	Not included
	Geddes et al 2010	12	-	Not analysed
	Events combined	**-122**	-	-
Depression	*Bowden et al 2000*	-29	-	NS
	Calabrese et al 2005	-17	-	Not included
	Geddes et al 2010	7	-	Not analysed
	Events combined	**-48**	-	-

NNH=number needed to harm (withdrawal due to unspecified adverse event); NNT=number needed to treat; NS=not significant; RR=risk ratio

Table 3. Lithium – efficacy estimates in maintenance treatment from observational studies

Paper	Comments
Kessing et al., 2017[8] Systematic review of observational studies of maintenance treatment of lithium vs other mood stabilisers	Lithium superior to other medicines in 8 of 9 monotherapy studies, and no significant difference vs valproate, olanzapine, quetiapine, and aripiprazole in one study. Specific findings were, as hazard ratio [HR] (95% CI) or NNT: Vs valproate: • GP outpatients (n=2136), time to treatment failure, HR 1.19 (1.09-1.31); • In- or outpatients (lithium 3549, valproate 719), time to treatment change, HR 1.86 (1.59-2.16), remained increased for index depressive, manic or mixed mood • In- or outpatients (lithium 3549, valproate 719), time to rehospitalisation, HR 1.33 (1.18-1.48), remained increased if hospitalised with manic/ mixed or depressed mood • Specialised outpatients (n=112), rate of recurrence, NNT 8 • GP outpatients (n=108), rate of sustained remission, NNT 5 Vs lamotrigine: • In- or outpatients (lithium, n=3518, lamotrigine, n=730), time to treatment change, HR 2.60 (2.23-3.04), remained increased for index depressive, manic or mixed mood • In- or outpatients (lithium, n=3518, lamotrigine, n=730), time to rehospitalisation, HR 1.45 (1.28-1.65), remained increased if hospitalised with depression. • Specialised outpatients (n=70), rate of recurrence, non-significant, NNT 25 Vs olanzapine: • GP outpatients (n=2841), time to treatment failure, HR 1.16 (1.05-1.28); • Outpatients in remission (n=338), relapse rate non-significant Vs quetiapine • GP outpatients (n=22240), time to treatment failure, HR 1.30 (1.18-1.44); • Specialised outpatients (n=80), rate of recurrence, NNT 6 Vs 'anticonvulsants' and/ or 'antipsychotics' • After hospital discharge, any mood state (n=135), p=0.002 vs atypical antipsychotics/ carbamazepine/ lamotrigine • Outpatients in remission (n=368), relapse rate vs anticonvulsants, NNT 9

	• US National MarketScan BD-I and BD-II (n=2743), time to change in medication: lithium 200 days (95% CI 155-245), anticonvulsants 90 days (95% CI 72-108), antipsychotics 90 days (95% CI 52-128)
Joas et al., 2017[9] Observational study of Swedish registry-linked data: within-individual analysis for hospitalisation rates	Overall, lithium was associated with a 34% reduction in the rate of admissions to a psychiatric hospital, valproate with 27%, olanzapine with 23%, lamotrigine with 22% and quetiapine with 18% compared with when the individuals were off the respective medicine. Within-individual efficacy estimates for the different mood states and for any episode are shown in the following excerpts from the article:

Table 2 Associations between different treatments and admission to psychiatric hospital estimated using within-individual models ($n = 35\,022$)[a]

	Psychiatric hospital admissions			
	All	Manic episodes	Depressive episodes	Mixed episodes
Medication, hazard ratios (95% CI)				
Lithium	0.66 (0.62–0.70)	0.56 (0.48–0.65)	0.61 (0.53–0.69)	0.56 (0.39–0.79)
Valproate	0.73 (0.67–0.79)	0.64 (0.53–0.78)	0.73 (0.59–0.89)	0.66 (0.44–0.99)
Carbamazepine	0.92 (0.77–1.10)	0.50 (0.29–0.86)	0.98 (0.64–1.48)	1.65 (0.59–4.62)
Lamotrigine	0.78 (0.73–0.84)	1.00 (0.78–1.28)	0.73 (0.63–0.84)	0.82 (0.53–1.27)
Quetiapine	0.82 (0.76–0.89)	0.73 (0.58–0.93)	0.66 (0.54–0.81)	0.92 (0.62–1.39)
Olanzapine	0.77 (0.72–0.83)	0.56 (0.46–0.67)	0.80 (0.68–0.93)	0.78 (0.52–1.17)
Events, *n*	23 383	4363	6637	973

a. All models adjusted for previous time spent in psychiatric in-patient care and age.

Table 3 Post-estimation comparisons of associations between treatment and psychiatric hospital admissions (within-individual analysis)[a]

	Hazard ratios (95% CI)					
	Lithium	Valproate	Carbamazepine	Lamotrigine	Quetiapine	Olanzapine
Lithium						
Valproate	0.90 (0.82–1.00)					
Carbamazepine	**0.71 (0.59–0.86)**	**0.79 (0.65–0.95)**				
Lamotrigine	**0.84 (0.76, 0.92)**	0.93 (0.84–1.04)	1.19 (0.98–1.43)			
Quetiapine	**0.80 (0.72–0.89)**	0.89 (0.79–1.00)	1.13 (0.92–1.36)	0.95 (0.85–1.06)		
Olanzapine	**0.85 (0.77–0.94)**	0.94 (0.84–1.05)	1.20 (0.99–1.45)	1.01 (0.91–1.13)	1.06 (0.95–1.19)	

a. A value below 1.0 indicates that the column treatment is superior to the row treatment. Results marked in bold are significant after false discovery rate *P*-value adjustment for multiple testing.

Anti-suicide effect

Two papers[4],[10] identified through the stated search strategies review RCT evidence for an anti-suicide effect associated with lithium in observational studies. One paper[11] reviews the effect of valproate on suicide in observational studies.

- Smith and Cipriani (2017)[4] – meta-review of systematic reviews
  - Cites observational study by Goodwin et al (2003) of US database (N=20638):
    Valproate vs lithium: significantly higher risk of suicide deaths, hazard ratio [HR] (95% CI) 2.7 (1.1-6.3), p=0.03; suicide attempts resulting in hospitalisation, HR 1.7 (1.2-2.3), p=0.002; suicide attempts ascertained in emergency department, HR 1.8 (1.4-2.2), p<0.001
    Carbamazepine vs lithium: significantly higher risk of suicide attempts resulting in hospitalisation 2.9 (1.9-4.4) p<0.001 but not of suicide deaths or emergency department visits.
  - Reports mainly on the systematic review by Cipriani et al (2013) which analysed 48 RCTs including participants with unipolar depression, bipolar disorder and schizoaffective disorder:
    Lithium vs placebo: reduced suicides, odds ratio [OR] (95% CI) 0.13 (0.03–0.66) and all-cause mortality, OR 0.38 (0.15–0.95); but not deliberate self-harm, OR 0.60 (0.27–1.32).
    Lithium vs active control: no significant differences except vs carbamazepine: lithium reduced deliberate self-harm, OR 0.14 (0.02–0.83).
  - Critiques another systematic review (Riblet et al. 2017) which did not find any benefit conferred by lithium, but which only analysed 6 RCTs including one methodologically flawed and underpowered study.

- Tondo and Baldessarini (2018)[10] – narrative review and meta-analysis
  - analysed 12 long-term RCTs in major depression and bipolar disorder participants (N=2044): Lithium vs placebo or active control: reduced suicides OR 0.222 (0.099–0.497), p < 0.0001 overall and in subgroup with only BD participants (6 RCTs, n=1407) OR 0.290 (0.108–0.784), p = 0.015.
- Chen et al (2019)[11] – systematic review and meta-analysis of effect of valproate on suicide
  - Random effects meta-analysis of 6 observational studies:
    Valproate vs placebo: No significant difference in incident rate of suicide attempts, relative risk [RR] (95% CI) 0.921 (0.383–2.215) or completed suicides RR 0.607 (0.180–2.043).
    Valproate vs carbamazepine: No significant difference in incident rate of suicide attempts RR 0.815 (0.453–1.466) or completed suicides RR 1.009 (0.410–2.484).

7. Alternative agents

Valproate, lamotrigine, olanzapine, quetiapine, antidepressants – see BD overview and individual motivations.

Prevention of any mood episode: Lithium is the only medicine with consistent evidence of efficacy vs placebo from RCTs (Butler et al., 2018), network meta-analysis (Miura et al., 2014), and observational studies with hard, patient-centred, outcomes (Kessing et al., 2017 and Joas et al., 2017). Thus, it is the only medicine with level I evidence in the overall management of BD.

Treatment and prevention of mania/ hypomania: Efficacy in acute mania is confirmed by Butler et al, with an NNT 5 which is competitive with that of olanzapine (NNT 6). RCT evidence for valproate in acute mania is inconclusive. While oral risperidone has efficacy in acute mania (NNT 4), it has no evidence of efficacy in maintenance treatment (see olanzapine motivation). For prevention of mania, RCT evidence alone is insufficient to support any medication. However, a direct calculation of RCT events for lithium yields an NNT 7 vs placebo, which is supported by evidence of efficacy from network meta-analysis and observational studies. While olanzapine has efficacy in prevention of mania, NNT 6 vs placebo, it is less efficacious than lithium in observational studies and has less efficacy in prevention of depression (no efficacy on network meta-analysis, NNT 18, and more time in subsyndromal depression in one head-to-head trial with lithium).

Treatment and prevention of depression: It is not clear whether the lack of evidence for lithium is related to a paucity of studies with participants at high risk of depression or due to a true lack of efficacy. For acute depression, no medicines had evidence of durable efficacy (at 12 weeks), but lithium *may* have efficacy when combined with adjunctive treatment (Butler et al). For prevention of depression, RCT evidence alone is insufficient to support any medication. Direct calculation from RCT events for lithium yields an NNT 16 vs placebo. However, lithium has evidence of efficacy from network meta-analysis and observational studies. In addition, it appears that lithium does reduce suicide risk, which is highest during depressive episodes. Valproate has no evidence of efficacy on network meta-analysis and no evidence of reduced suicide risk. Quetiapine has evidence of efficacy on acute depression at 8 weeks (Selle et al 2014) and evidence for prevention of depression on network meta-analysis but has significantly less efficacy than lithium from real-world observational studies.

8. Interpretation of the evidence and comments

Taking the overall evidence of efficacy for lithium together with neuroprotective and other possible illness-related benefits, lithium is recommended as first-line treatment of BD, with the following considerations:

- Adjunctive treatment may be required in acute mania with severe behavioural disturbance and in acute depression.
- Combination treatment may be required for those with recurrent manic episodes and for prevention of depression.
- Alternative treatment will be required for those who have poor access to laboratory monitoring, are at risk of toxicity (e.g. severe medical illness or substance use causing intermittent severe dehydration, renal dysfunction, drug-drug interactions with other chronic medication), or are at risk of repeated non-compliance with lithium.[12]

- Pre-pregnancy counselling and alternative treatment will be required for women in the reproductive age group in whom risks to the fetus are unacceptable. Lithium has been used safely and effectively in pregnancy for prevention of relapse.[13] However, teratogenicity is a concern. Combining data from 6 international birth cohorts, comparing women on lithium (n=727) with a reference group of pregnant women with any mood disorder (n=21397), Munk-Olsen et al. (2018)[13] found 1st trimester lithium exposure associated with an increased risk of major anomalies in general, (pooled adjusted Odds Ratio [aOR] 1·71, 95% CI 1·07–2·72, NNH 25 from simple calculation of events), but not with major cardiac malformations, (aOR 1·54, 95% CI 0·64–3·70). In-utero lithium exposure was also associated with an increased rate of neonatal hospital admissions in first 28 days after birth, (aOR 1·62, 95% CI 1·12–2·33, NNH 8 from reported events), however this was non-significant when compared only to those in the reference group with a diagnosis of bipolar disorder (aOR 0.97, 95% CI 0.54–1.75).

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 [ ]	Systematic reviews by: - Butler et al, 2018 - Miura et al, 2014
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. Prevention of mania: valproate, olanzapine Prevention of depression: lamotrigine as adjunctive, quetiapine	
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/ month: **Medicine** / **ZAR** Lithium 200 mg daily / 34.44 Lithium 600 mg daily / 172.22 *Contract circular HP09-2016SD Lithium 400 mg 100 tabs = R229.63 (Accessed April 2019) **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

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 this evidence review, the Adult Hospital Level Committee reccomends lithium as first-line therapy for any mood episode, acute treatment and prevention of relapse of bipolar disorder; with caveats – counselling required for pregnancy, not recommended in those at risk of lithium toxicity or where lithium will be abruptly discontinuation (as this precipitates mania), previous non-response or poor tolerability). Lithium combination therapy may be beneficial in select patients.

Rationale: Evidence of efficacy of lithium for acute mania and closed-loop network analysis shows that lithium is efficacious for prevention of any mood episode, mania, and depression; though lithium is poorly tolerated. Naturalistic data suggests lithium is superior vs other monotherapy in prevention of rehospitalisation and recurrence of BD with manic, mixed or depressive index episodes. The benefit of reducing maternal and neonatal morbidities in bipolar disorder considered to outweigh the congenital risk of lithium; though informed consent would be viable.

Level of Evidence: II Systematic reviews and meta-analyses of placebo-controlled RCTs [2, 3], Observational studies [8, 13]

Review indicator:

Evidence of efficacy [ ] Evidence of harm [X] Price reduction [ ]

VEN status:

Vital [ ] Essential [X] Necessary [ ]

NEMLC MEETING OF 11 JULY 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee (see above).

Monitoring and evaluation considerations

National, provincial and district level systems for safety monitoring are strongly recommended.

Research priorities

References:

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