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

1. Executive Summary

Date: 6 June 2017
Medicine (INN): Clotiapine injection
Medicine (ATC): N05AH06
Indication (ICD10 code): Acute aggressive disruptive behaviour (R45.1/4/5/6/F60.3)
Patient population: Adults
Level of Care: Primary and secondary level
Prescriber Level: Medical doctor
NNT: n/a
Current standard of Care: Chlorpromazine injection / Haloperidol+Promethazine
Motivator/reviewer name(s): Dr Lesley Robertson
PTC affiliation: Gauteng Provincial PTC

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

Dr Lesley Robertson

3. Author affiliation and conflict of interest details

Affiliation: University of Witwatersrand; Affiliated to South African Society of Psychiatrists; Committee member of the Adult Hospital Level Expert Review Committee (2017-2019); Co-opted to support the Primary Health Expert Review Committee (2016-2018).

Conflicts of interest: Dr Reddy Laboratories annual sponsorship of Public Sector Psychiatry Forum (SASOP); Honararium from Sanofi Aventis (2015) channelled to South African Society of Mental Health and Deafness via SASOP.

4. Introduction/Background

As chlorpromazine injection has not been available on contract since 2014 (erratic availability of chlorpromazine from sole supplier) there is a need for an alternative to Haloperidol+Promethazine in the acute management of aggressive and disruptive patients at PHC and hospital level (Adult). (The current Adult Hospital Level STGs and EML, 2015 edition, recommends chlorpromazine injection when haloperidol injection is not available).

5. Purpose/Objective

- **P:** Adults with acute aggressive and disruptive behaviour
- **I**: Chlorpromazine injection
- **C**: Clotiapine injection
- **O**: Rapid tranquilisation, stabilisation

6. Methods

Search strategy:

The Tripdatabase was searched, using the following search strategy "chlorpromazine AND clotiapine" and articles were restricted to systematic reviews and controlled trials.

Two Cochrane reviews and two controlled trials were retrieved.

Excluded studies:

Author, date	Type of study	Reason for exclusion
Brambilla et al, 1987[i]	Controlled trial	Not relevant
Mazhari et al, 2017[ii]	Systematic review	Chronic schizophrenia
Geller et al, 2005[iii]	Controlled trial	Chronic schizophrenia

Evidence synthesis and quality:

Author, date	Study	n (population)	Comparators	Primary outcome	Effect sizes	Comments
Carpenter, 2004[iv]	Systematic review	5 RCTs (n=261)	Clotiapine vs other antipsychotics (chlorpromazine, perphenazine, trifluoperazine and zuclopenthixol acetate) or benzodiazepines (lorazepam). Only 3 RCTs compared IM formulations: - Clotiapine IM vs trifluoperazine IM - Clotiapine IM + haloperidol IM vs lorazepam IM + haloperidol IM - Clotiapine IM vs Zuclopenthixol acetate, IM.	• No important global improvement. • Proportion of people ready for hospital discharge. • Need for antiparkinsonian Treatment. • Control aggressive/violent outbursts for people also treated with haloperidol IM	• n = 83, 3 RCTs, RR 0.82 CI 0.22 to 3.05, $I^2$58%. Clotiapine was comparable to chlorpromazine, oral; perphenazine, oral; or trifluoperazine, IM. • n = 49, 1 RCT, RR 1.04 95%CI 0.96 to 2.12 Note: clotiapine, oral vs chlorpromazine, oral. • n = 38, RR 0.43 95%CI 0.02 to 0.98 Note: Clotiapine, IM shown to have less EPSE vs zuclopenthixol acetate, IM. • WMD -3.36 95%CI -8.09 to 1.37, NS Note: Lorazepam, IM vs clotiapine, IM	Low attrition rate reported in RCTs. Studies were old, of low methodological quality and had high heterogeneity. Not much data could be pooled due to skew or inadequate presentation of results Direct comparison of clothiapine vs chlorpromazine was limited to one study which used oral formulations of both medicines – findings need to be extrapolated to IM.

7. Alternative agents

Antipsychotics:

- Zuclopenthixol acetate 50mg/ml injection. However, there are safety concerns due to its long half-life (36 hours) and risk of EPSE which is equivalent to that of haloperidol IM. It is recommended that this is restricted for use in hospital psychiatric wards (Regional Hospital level and above).

Refer to Medicine review: Zuclopenthixol acetate for acute psychosis in adults, 6 June 2017.

Note: Injectable SGAs such as olanzapine injection and aripiprazole injection are alternative options but are precluded due to cost.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [ ] Not confident [X] Uncertain [ ]</td><td></td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [X] No [ ]

List the members of the group.
• Zuclopenthixol acetate
Note: Use is recommended to be restricted to inpatients of psychiatric units because of the safety concerns related to its long half-life.

List specific exclusion from the group:</td><td>Rationale for therapeutic alternatives included:

References:

Rationale for exclusion from the group:

References:</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>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 [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [x] Uncertain [ ]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Clotiapine 10mg/ml, 40mg IM 8 hourly</td><td>R59.40</td></tr><tr><td>Zuclopenthixol acetate 50mg/ml, 50 mg , IM as a single dose</td><td>R77.24</td></tr></table>Contract circular HP06-2017SVP:
- clotiapine 10mg/ml; 4 ml = R19.80
- zuclopenthixol acetate 50mg/ml; 1 ml = R77.24
Additional resources:
n/a</td></tr>
</table>

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 the above appraisal of the evidence, the Adult Hospital Level and Primary Health Care Expert Review Committees recommend that chlorpromazine injection is replaced by clotiapine injection for use in rapid tranquillisation of aggressive/ disruptive patients when the haloperidol + promethazine is not available.

Rationale: Available evidence overall is very low quality and insufficient evidence to recommend one injectable antipsychotic over another as an alternative to haloperidol + promethazine. The decision to use clotiapine IM as an alternative to chlorpromazine IM is related to reliability of supply, possible safety considerations in comparison to zuclopenthixol acetate and cost.

Level of Evidence: II Low quality systematic review

NEMLC RECOMMENDATIONS:

NEMLC Meeting:14 December 2017[v]:

Clotiapine, IM: There are pragmatic implications for long-acting psychotic use in the emergency setting in PHC, prior to referral to the secondary level. The PHC STG does provide an alternative option to haloperidol, benzodiazepine and orthostatic hypotension associated with clotiapine is a concern.

NEMLC Recommendation: Clotiapine, IM not be recommended for primary level EML, but be considered for the Adult Hospital level EML.

NEMLC Meeting: 11 July 2019[vi]

Alternate option to haloperidol, IM (clotiapine) not be included in the STG; as the STGs generally do not recommend alternative options due to supply challenges. The information is disseminated to health care workers via NDoH circular and should preferably be included on the Therapeutic Interchange database.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
	X	

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Safety monitoring of all rapid tranquillisation is recommended.

Research priorities

The extent of aggressive and violent behaviour and its related its factors at primary and secondary level is needed to inform future public health interventions.

References:

[i]Brambilla F, Facchinetti F, Petraglia F, Smeraldi E, Bellodi L, Brancato V, Genazzani AR. Effects of neuroleptic treatments on peripheral opioid secretion. Neuropsychobiology. 1987;18(2):68-73.

[ii]Mazhari S, Esmailian S, Shah-Esmaeili A, Goughari AS, Bazrafshan A, Zare M. Chlorpromazine versus clotiapine for schizophrenia. Cochrane Database Syst Rev. 2017 Apr 7;4:CD011810.

[iii]Geller V, Gorzaltsan I, Shleifer T, Belmaker RH, Bersudsky Y. Clotiapine compared with chlorpromazine in chronic schizophrenia. Schizophr Res. 2005 Dec 15;80(2-3):343-7.

[iv]Carpenter S, Berk M, Rathbone J. Clotiapine for acute psychotic illnesses. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD002304.

[v] Minutes of the NEMLC meeting of 14 December 2017.

[vi] Minutes of the NEMLC meeting of 11 July 2019