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

1. Executive Summary

Date: 6 June 2017
Medicine (INN): Zuclopenthixol acetate
Medicine (ATC): N05AF05
Indication (ICD10 code): B24
Patient population: Adults with acute psychosis
Level of Care: Primary
Prescriber Level: Nursing practitioner or medical doctor
NNT: n/a
Current standard of Care:
Motivator/reviewer name(s): Dr Lesley Robertson/Ms Trudy D Leong
PTC affiliation: Gauteng Provincial PTC

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

Dr Lesley Robertson
Ms Trudy D Leong

3. Author affiliation and conflict of interest details

Dr Lesley Robertson:
Affiliation: University of Witwatersrand, Affiliated to South African Society of Psychiatrists.
Conflicts of interest: Dr Reddy Laboratories annual sponsorship of Public Sector Psychiatry Forum (SASOP);

Ms Trudy Leong:
Affiliation: NDoH; Essential Drugs Programme - Secretariat for the Adult & PHC Technical Sub-Committees of Conflicts of interest: None declared.

a. Background

Acute aggression should essentially be managed with medicines that have rapid onset of action, low frequency of administration and few adverse effects[i]. Zuclopenthixol acetate has to date been recommended in the PHC and Adult Hospital Level STGs, as it has been determined to have these properties.

However, the 2015 NICE guidelines for violence and aggression[ii] do not include zuclopenthixol acetate in medication algorithm for rapid tranquillisation. Maudsley Prescribing Guidelines[iii] recommend that zuclopenthixol acetate be reserved only for those who remain uncontained after having received repeated antipsychotic and sedative injections. It may therefore be of use for selected patients in psychiatric wards.

The review of the evidence was recommended to determine if zuclopenthixol acetate injection should be removed from the PHC and Adult Hospital STGs. Factors considered included the treatment setting for these guidelines (there is no available evidence for zuclopenthixol acetate injection in

undifferentiated patients with aggressive or disruptive behaviour in the primary care or district hospital setting); as well as the possibility of harm when used in such patients.

Zuclopenthixol acetate 50mg/ml is an injectable typical antipsychotic which reaches a half-life concentration at 36 hours after injection with a duration of action of 48 – 72 hours. Adverse drug effects include acute dystonic reactions and neuroleptic malignant syndrome (NMS).[iv] Due to its longer duration of action it is not possible to "stop the medication" in the case of a severe adverse effect. Essentially not recommended for use in neuroleptic naïve individuals or those with a comorbid medical illness, pregnancy or a history of extra-pyramidal side effects.[iii]

b. PICO/Objective

-P *(patient/population):* Adults with acute psychosis
-I *(intervention):* zuclopenthixol acetate
-C *(comparator):* haloperidol or other antipsychotics
-O *(outcome):* rapid tranquillisation and adverse effects

What is the effectiveness and safety of zuclopenthixol acetate in adults presenting with acute psychosis compared to haloperidol?

6. Methods

Search 1

Database: Cochrane library
Search terms: "Zuclopenthixol acetate" and "acute psychosis" with word variations/MESH terms
Results: 30 studies retrieved, of which 3 were duplicates
Excluded studies:

Author, date	Reason for exclusion
Kumar et al, 2005	Not relevant - oral zuclopenthixol
Ostinelli et al, 2017; Dold et al, 2015;Cipriani et al, 2006; Huf et al, 2016; Khushu et al, 2016; Quraishi et al, 1999	Not relevant - haloperidol
Berk et al, 2015	Not relevant - clotiapine
Gillies et al, 2013	Not relevant - benzodiazepines
Khokhar et al, 2016	Not relevant - droperidol
Du et al, 2017	Not relevant - de-escalation
Vangala et al, 2012	Not relevant - loxapine inhaler
Webb et al, 2004	Not relevant - pregnancy, postpartum
Belgamwar et al, 2005	Not relevant - olanzapine
Irving et al, 2006	Not relevant - polyunsaturated fatty acids
Laurier et al, 2014; Lamure et al, 2003	Not relevant - economic evaluation
Uys et al, 1996	Not relevant - zuclopenthixol vs clotiapine
McCreadie et al, 1995	Not relevant - risperidone vs haloperidol
Lacey et al, 2015	Not relevant - zuclopenthixol dihydrochloride. oral

Search 2

Database: Pubmed
Search strategy: *("clopenthixol acetate ester"[Supplementary Concept] OR "clopenthixol acetate ester"[All Fields] OR "zuclopenthixol acetate"[All Fields]) AND (acute [All Fields] AND ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]))*
Results: 23 studies retrieved, with 3 considered as duplicates
Excluded studies:

Author, date	Reason for exclusion
Tucker et al, 2016	Not relevant - case report
Powney et al, 2012	Not relevant - haloperidol
Khalifa, 2004	Not relevant - in vivo study

Carpenter et al, 2001; 2004	Not relevant - clotiapine
Romain et al, 1996; Bttig, 1988; Bourdouxhe et al, 1987	French
Laurier et al, 2014	Not relevant - economic evaluation
Fitzgerald, 1999	Not relevant - social factors
Predescu, 1991; Matar, 1990; Lowert, 1989; Amdisen et al, 1987	Not relevant - open label, not randomised
Schlosberg et al, 1991	Not relevant - open pilot study
Balant et al ,1989; Amdisen et al, 1986	Not relevant - open label, PK/pharmacodynamic study
Baastrup, 1997	Included in Dold et al review (see evidence synthesis table)
Taymeeyapradit, 2002	Included in Jayakody et al review (see evidence synthesis table)

Search 3

Database: Google scholar

a. Evidence synthesis

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Jayakody et al, 2012[i]	Systematic review	9 RCTs	Adult patients with acute schizophrenia and similar serious mental illnesses	Zuclopenthixol acetate, IM vs standard medication (antipsychotics)	**1 Tranquillisation** (feeling of calmness and/or calm, non-sedated behaviour) **2. Sedation** (sleepiness and drowsiness) **3. Global state** **4. Mental state** **5. Adverse effects**	**1.** No data for the primary outcome, **tranquillisation.** **2. Sedation:** i. Zuclopenthixol acetate comparable to haloperidol at 2 hours: (n = 40, 1 RCT, RR 0.60, 95% CI 0.27 to 1.34). **3. Global state:** (Zuclopenthixol acetate vs standard medicines) i. Requiring supplementary medication- antipsychotics (Follow-up: 3-9 days): n = 134, 3 RCTs, RR 1.49, 95% CI 0.97 to 2.30) ii. Requiring supplementary medication- benzodiazepines: n = 50, 1 RCT, RR 0.03, 95% CI 0.00 to 0.47. iii. Requiring ≥ 3 injections over seven days (Zuclopenthixol acetate vs haloperidol, IM: n = 70, 1 RCT, RR 0.39, 95% CI 0.18 to 0.84, NNT 4, CI 3 to 14). **4. Mental state**: No data on more episodes of aggression or harm to self or others. **5. Adverse effects**: i. One trial (n = 148) reported no significant difference in adverse effects between zuclopenthixol acetate, IM vs haloperidol, IM groups at one, three and six days (RR 0.74, 95% CI 0.43 to 1.27 ii. Movement disorders - dystonia (spasmodic postural disorder) - by 24 hours: RR 0.68, 95% CI 0.34 to 1.36; 3 studies, n =242. iii. No difference between treatments for leaving the study before completion (n = 522, RR 0.85, 95% CI 0.31 to 2.31). iv. One study reported no difference in adverse effects and outcome scores, when high dose (50-100 mg/injection) zuclopenthixol acetate was compared with low dose (25-50 mg/injection) zuclopenthixol acetate.	• ITT analysis • Overall the quality was poor (RCTs of low methodological quality) • No data relating directly to tranquillisation. • RCT suggest that lower doses of zuclopenthixol acetate may be adequate to sedate agitated patient. • RCTs in the hospital setting only; participants had schizophrenia or affective psychoses (mania). - no evidence for use in emergency setting. • Haloperidol doses higher than those used clinically today. • No difference in reported adverse events. The only advantage of zuclopenthixol acetate was the need for fewer coercive injections over the same time period.
Dold et al, 2015[v]	Systematic review	• 63 RCTs, n=3675 Haloperidol vs first generation antipsychotics (FGA) • Sub-analysis (haloperidol vs zuclopenthixol): 2 RCTs; n=103	Patients with schizophrenia in the inpatient and outpatient settings	Overall: Haloperidol vs first generation antipsychotics (FGA) Subgroup analysis: Haloperidol, IM vs zuclopenthixol acetate, IM	Clinically important response to treatment (short term)	• RR 0.94 [95% CI 0.70 to 1.28], I^2=46% • No statistically significant between-group differences (haloperidol, IM vs FGA) due to adverse effects; though haloperidol produced less akathisia in the medium term: RR 0.31, 95% CI 0.16, 0.60.	• Limited data of low quality (Bias: 1 RCT was and open study - selection bias; reporting bias; attrition bias & other RCT had inadequate details to determine bias). • Data heterogeneous • Participants diagnosed with schizophrenia and other types of schizophrenia-like psychoses.

Efficacy:
Available evidence suggesting that zuclopenthixol acetate, IM is comparable to haloperidol, IM for treatment of acute psychosis in the disturbed patients, is limited and of low quality.

Safety:
Limited RCT evidence suggests no difference in side-effects between haloperidol, IM vs. zuclopenthixol acetate, IM for management of acute psychosis. However, the safety concern of long-acting zuclopenthixol acetate, IM in the acute setting was noted and a google scholar search of relevant safety registry data, case series and case reports was done.

Regarding the adverse effect of NMS, zuclopenthixol acetate was implicated in 3 of 4 case reports of NMS in adolescents treated for psychosis in the Western Cape.[vi] This adverse effect may have been exacerbated by concomitant use of other antipsychotics, use of illicit substances and vulnerability as adolescents.

Zuclopenthixol-induced NMS reported in an adolescent girl without pyrexia following a single depot injection of 200 mg of zuclopenthixol.[vii]

b. Evidence quality: Overall quality of evidence is low. Cochrane reviews state the possibility of industry sponsorship bias.

7. Alternative agents:
- Haloperidol, IM + Promethazine, IM
- Clotiapine, IM

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:	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: X Harms outweigh benefits: Benefits = harms or Uncertain:	

<table>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:

Yes   No
[ ]   [X]

List the members of the group.

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   No   Uncertain
[X]   [ ]   [ ]</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:

<table><tr><th>Medicine</th><th>Cost (ZAR)*</th></tr><tr><td>Zuclopenthixol Acetate 50mg/mL 1 mL</td><td>R 77.238</td></tr></table>*Contract circular HP06-2017SVP
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes   No   Uncertain
[ ]   [X]   [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?

Yes   No   Uncertain
[X]   [ ]   [ ]</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 reveiw, the Adult Hospital Level and Primary Health Care Committees reccommend that zuclopenthixol acetate be deleted from the PHC EML, but retained in the Adult Hospital Level EML for use at regional hospitals, as specialist prescribed to manage acute psychosis in adults.

Rationale: Zuclopenthixol acetate has been removed with warnings from guidelines for rapid tranquillisation. The reason is that has no advantage over haloperidol except for needing fewer coercive injections over the next 72 hours, due to its very long half-life. There have been reports of associated neuroleptic malignant syndrome and the long half-life provides additional challenges.

Level of Evidence: III Guidelines, Case series, Expert opinion

Review indicator: n/a

Evidence of efficacy	Evidence of harm	Price reduction

VEN status:

Vital	Essential	Necessary
X		

Monitoring and evaluation considerations

Research priorities

References

[i] Jayakody K, Gibson RC, Kumar A, Gunadasa S. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Cochrane Database Syst Rev. 2012 Apr 18;(4):CD000525.

[ii] NICE Clinical Guideline. Violence and aggression: short-term management in mental health, health and community settings 2015. Available from: nice.org.uk/guidance/ng10.

[iii] The Maudsley Prescribing Guidelines in Psychiatry. 12th ed: WILEY Blackwell; 2015.

[iv] SAMF, 2016

[v] Dold M, Samara MT, Li C, Tardy M, Leucht S. Haloperidol versus first-generation antipsychotics for the treatment of schizophrenia and other psychotic disorders. Cochrane Database Syst Rev. 2015 Jan 16;1:CD009831.

[vi] Henderson T. Neuroleptic malignant syndrome in adolescents: four probable cases in the Western Cape. S Afr Med J. 2011;101(6):405-7.

[vii] Erermis S, Bildik T, Tamar M, Gockay A, Karasoy H, Ercan ES. Zuclopenthixol-induced neuroleptic malignant syndrome in an adolescent girl. Clin Toxicol (Phila). 2007;45(3):277-80.