



health

Department: Health
REPUBLIC OF SOUTH AFRICA



Reference: AMD/07Aug23

Enquiries:

Stock queries:

Ms Babalwa Melitafa

E-mail: Babalwa.Melitafa@health.gov.za

Clinical queries:

Essential Drugs Programme

E-mail: SAEDP@health.gov.za

NOTICE: RECOMMENDED THERAPEUTIC ALTERNATIVES FOR CLONAZEPAM AND LORAZEPAM INJECTIONS

The Adult Hospital Level and Paediatric Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) currently recommends the use of clonazepam 1mg/ml injection and lorazepam 4mg/ml injection 1ml for various indications.

There are currently supply challenges with clonazepam and lorazepam injections (both items are not on a national contract and were previously being supplied *via* national quotation).

Diazepam and Midazolam injections and various **oral benzodiazepines** are available as alternatives for various indications as listed in the STGs and EML. Please refer to the different relevant sections of the Adult Hospital level and Paediatric Hospital Level STGs and EML for comprehensive guidance on management of various indications where these medicines are recommended.

The following indications are however specifically highlighted for your attention:

Adult Hospital Level STGs and EML

Indication: Hospital Level (Adults)	Therapeutic alternatives to clonazepam 1mg/ml & lorazepam 4mg/ml injections:
<p>15.1 AGGRESSIVE DISRUPTIVE BEHAVIOUR IN ADULTS * (Refer to note below)</p>	<p>MEDICINE TREATMENT– Rapid Tranquillisation The goal of rapid tranquillisation is to calm the patient so that risk to self or others is minimised and the underlying condition may be managed.</p> <div style="border: 1px solid black; padding: 5px; margin: 10px 0;"> <p style="text-align: center;">CAUTION</p> <ul style="list-style-type: none"> » Rapid tranquillisation may cause cardiovascular collapse, respiratory depression, acute dystonic reactions, and neuroleptic malignant syndrome. » Pregnant women, elderly, intellectually disabled and those with comorbid medical conditions and/or substance use are at highest risk. » Late pregnancy: neonatal sedation or extra-pyramidal side effects may occur. » Write out single prescriptions and review between each prescription. » Allow at least 30 – 60 minutes between prescriptions. » An emergency trolley, airway, bag, oxygen and intravenous line must be available. </div> <ul style="list-style-type: none"> » Monitor vital signs closely during and after medicine administration. » The safest route of administration of benzodiazepines is oral followed by IM with the IV route having the highest risk of respiratory depression and arrest. Use the safest route possible. » Use olanzapine as 1st line (i.e., without oral benzodiazepine): <ul style="list-style-type: none"> o In pregnancy, the frail and elderly, or where respiratory depression is a concern. o Where aggression is clearly caused by psychosis » Do not use depot antipsychotic injections (e.g., flupenthixol decanoate or zuclopenthixol decanoate injections) in rapid tranquillisation.

Indication: Hospital Level Adults	Therapeutic alternatives to clonazepam 1mg/ml & lorazepam 4mg/ml injections:
	<p>Offer oral benzodiazepine treatment:</p> <ul style="list-style-type: none"> ▪ Benzodiazepines: <ul style="list-style-type: none"> • Lorazepam, oral, 0.5–2 mg, immediately. <p>OR</p> <ul style="list-style-type: none"> • Clonazepam, oral, 0.5–2 mg, immediately. <p>OR</p> <ul style="list-style-type: none"> • <i>Diazepam, oral, 5–10 mg, immediately.</i> <p>OR</p> <ul style="list-style-type: none"> • <i>Midazolam, oral or buccal, 7.5–15 mg, immediately.</i> <p><u>Inadequate response to oral benzodiazepine (after 30–60 minutes) or oral treatment refused, administer parenteral or oro-dispersible olanzapine:</u></p> <ul style="list-style-type: none"> • Olanzapine, orodispersible tablet/ IM, 5–10 mg immediately <ul style="list-style-type: none"> ○ Repeat after 30–60 minutes if needed. <p>Note:</p> <ul style="list-style-type: none"> ○ Use lower doses (2.5–5mg) in elderly, frail, or medically unwell patients. ○ Repeated doses may result in excessive sedation. <p><u>If previous intolerance to olanzapine (e.g., previous neuro-malignant syndrome) administer parenteral benzodiazepine</u></p> <ul style="list-style-type: none"> • Lorazepam, IM, 0.5–2 mg, immediately. <p>OR</p> <ul style="list-style-type: none"> • <i>Midazolam, IM, 7.5–15 mg immediately.</i> <p>OR</p> <ul style="list-style-type: none"> • Clonazepam, IM, 0.5–2 mg, immediately. <p>Note:</p> <ul style="list-style-type: none"> ○ To avoid inappropriate repeat dosing allow at least 30 minutes for the oral/IM medication to take effect. ○ Repeated IM doses of benzodiazepines may result in toxicity owing to accumulation. ○ Lorazepam IM has slower onset of sedation than midazolam IM (32 vs 18 minutes) and longer duration of sedation (217 vs 82 minutes). ○ Clonazepam oral or IM may be used if longer duration of sedation is required. Onset of action may be 30-60 minutes, time to maximum concentration is 1-4 hours. Long half-life (18-50 hours) increases risk of accumulation. Allow at least 12 hours between repeat doses. <p><u>Under specialist care in psychiatric wards:</u></p> <ul style="list-style-type: none"> • Zuclopenthixol acetate, IM, 50–150 mg every 2–3 days (specialist/specialist consultation). <ul style="list-style-type: none"> ○ Maximum dose is 400 mg over a two-week period. <p><u>If alcohol use is suspected:</u></p> <p>ADD</p> <ul style="list-style-type: none"> • Thiamine, oral, 300 mg immediately and daily for 14 days.
<p>15.8.1.1 ALCOHOL WITHDRAWAL DELIRIUM (DELIRIUM TREMENS) ** (Refer to note below)</p>	<p>MEDICINE TREATMENT</p> <p>Administer medicine doses according to severity of symptoms. These patients may require high doses of benzodiazepines because of hepatic enzyme induction.</p> <ul style="list-style-type: none"> ▪ Benzodiazepines, e.g.: Diazepam, slow IV, 10 mg (Not IM). <ul style="list-style-type: none"> ○ Repeat dose after 5–10 minutes if required. ○ If this dose is not sufficient, use 10 mg every 5–10 minutes for another 1–2 doses. ○ If patient is not yet sedated, continue with doses of 20 mg until this occurs. Usual initial dose is 10–20 mg, but up to 60 mg is occasionally required. <p>OR</p> <p><u>Where intravenous access is not possible:</u></p> <p>Clonazepam, IM, 2 mg as a single dose.</p> <ul style="list-style-type: none"> ○ If no response, repeat dose after 60 minutes until patient is sedated. ○ Repeat dose regularly to maintain mild sedation. <p>OR</p> <ul style="list-style-type: none"> • Lorazepam, IM, 1–4 mg every 30–60 minutes until patient is sedated. <ul style="list-style-type: none"> ○ Repeat dose regularly to maintain mild sedation. <p><u>Once patient is sedated, i.e., light somnolence, maintain mild sedation with:</u> Diazepam, oral, 5–20 mg.</p>

Indication: Hospital Level (Adults)	Therapeutic alternatives to clonazepam 1mg/ml & lorazepam 4mg/ml injections:
	<ul style="list-style-type: none"> ○ Repeat dose regularly to maintain mild sedation. <div style="border: 1px solid black; padding: 5px; text-align: center;"> <p>CAUTION</p> <p>Benzodiazepines, especially diazepam IV, can cause respiratory depression. Monitor patients closely as benzodiazepines can exacerbate an abnormal mental state or mask important neurological signs of deterioration.</p> </div>

***Note: Medicine Treatment for Aggressive Disruptive Behaviour:**

- The medicine treatment for Aggressive Disruptive Behaviour indicated in the table above is taken from the recently approved Mental Health Conditions and Substance Misuse chapter of the Adult Hospital Level STGs and EML (approved at NEMLC meeting held on 20 July 2023). The updated chapter will be edited prior to finalisation and circulation to all stakeholders. This updated chapter forms part of the 2024 edition of the Adult Hospital Level STGs and EML.
- Olanzapine IM/oro-dispersible tablets were ratified for addition to the medicine treatment of Aggressive Disruptive Behaviour.

****Note: Medicine Treatment for Alcohol Withdrawal Delirium:**

- To be managed with oral diazepam as far as possible (in most cases) if unable to take oral medication, it is recommended to use slow IV infusion.
- **Do not use olanzapine IM in the management of alcohol withdrawal.** Olanzapine IM may increase risk of respiratory depression if combined with parenteral benzodiazepines particularly if alcohol has been consumed.
- Due to its short duration of action, **midazolam IM is not recommended** for alcohol withdrawal delirium.

Paediatric Hospital Level STGs and EML

Indication: Hospital Level (Paediatrics)	Therapeutic alternatives to clonazepam 1mg/ml inj 1ml & lorazepam 4mg/ml inj 1ml
14.1 Sedation of an acutely disturbed child or adolescent	<p>For children under the age of six years: Sedation with psychotropic agents should only be considered in extreme cases and only after consultation with a specialist.</p> <p>For children over the age of six years:</p> <ul style="list-style-type: none"> • Lorazepam, oral If not appropriate consult with a specialist <p>For Adolescents consider following adult recommendations above.</p>
14.13.3.2 Alcohol withdrawal delirium	<p>Benzodiazepines:</p> <ul style="list-style-type: none"> • Diazepam, slow IV, 10 mg (not IM due to erratic absorption). <ul style="list-style-type: none"> ○ Repeat dose after 5–10 minutes if required. ○ If this dose is not sufficient, use 10 mg every 5–10 minutes for another 1–2 doses. ○ If patient is not yet sedated, continue with doses of 20 mg. ○ Usual initial dose is 10–20 mg, but up to 60 mg is occasionally required. <p>Where intravenous access is not possible:</p> <ul style="list-style-type: none"> • Consult specialist. • For adolescents consider following adult recommendations above

Procurement of Diazepam and Midazolam

NSN	Product	Supplier	Contract
180076401	Midazolam; 5mg/5ml; Injection; 5ml	Accord Healthcare (Pty) Ltd Adcock Ingram Critical Care (Pty) Ltd	HP06-2021SVP
180076404	Midazolam; 15mg/3ml; Injection; 3ml	Adcock Ingram Critical Care (Pty) Ltd Pharma-Q (Pty) Ltd	HP06-2021SVP
180075798	Diazepam; 10mg/2ml; Injection; 2ml	Pharma-Q (Pty) Ltd	HP06-2021SVP
222001090	Diazepam; 5mg; Tablet; 14 Tablet	Innovata Pharmaceuticals (Pty) Ltd	HP09-2023SD

Note:

- The National Department of Health will advise when the supply of clonazepam and lorazepam injections are resumed.
- The procurement details for Olanzapine inj/oro dispersible tablet will follow in due course.

Circular dissemination

Provinces and Healthcare Facilities are requested to distribute and communicate this information in consultation with the Pharmaceutical and Therapeutics Committees and all other relevant stakeholders.

Kind regards

K Jamaloodien

MS K JAMALOODIEN
CHIEF DIRECTOR: SECTOR-WIDE PROCUREMENT
DATE: 08/08/2023