



## MONOGRAPH

### Clozapine

|                |  |
|----------------|--|
| Scope (Staff): | Medical, Pharmacy, Nursing                                       |
| Scope (Area):  | All Clinical Areas, Community Child and Adolescent Mental Health |

#### Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this [DISCLAIMER](#)

**! HIGH RISK MEDICINE !**

#### QUICKLINKS

|   |                                |                            |                              |
|---|--------------------------------|----------------------------|------------------------------|
| <a href="#">Dosage/Dosage Adjustments</a> | <a href="#">Administration</a> | <a href="#">Monitoring</a> | <a href="#">Interactions</a> |
|---|--------------------------------|----------------------------|------------------------------|

#### DRUG CLASS

Clozapine is a [High Risk Medicine](#). Clozapine is regulated by the Therapeutic Goods Association (TGA), under the Highly Specialised Drugs Program.<sup>1</sup>

Clozapine is an atypical antipsychotic. Although the exact mechanism of action of clozapine is unknown, the therapeutic effect is thought to occur in part from inhibition of central dopamine-2 (D2) and serotonin 5-HT<sub>2A</sub> receptors. Clozapine has a high affinity for 5-HT<sub>2A</sub> receptors compared to D2 receptors, which may contribute to its efficacy in treating both positive and negative symptoms of schizophrenia.<sup>2-5</sup>

Clozapine is also a muscarinic-receptor antagonist and exhibits potent inhibitory binding affinity at histamine-1 (H<sub>1</sub>) and alpha-1 adrenoceptors.<sup>3, 4, 5</sup>

#### INDICATIONS AND RESTRICTIONS

- Clozapine is not listed on the Paediatric State-wide Medicines Formulary. All prescribing requires prior approval from the CAHS Drug & Therapeutics Committee.**
- Clozapine has significant restrictions placed on its use due to the risk of agranulocytosis and other serious side effects. Clozapine is rarely used within Child and Adolescent Mental Health Services. When Clozapine is initiated, the Clozapine Patient Management System (CPMS) protocol must be adhered to. The CPMS is currently provided by ClopineCentral™.<sup>6, 7</sup>

- Clozapine is intended as third line treatment for chronic schizophrenia refractory to treatment with other medications where the patient has had an adequate trial of at least two other antipsychotic drugs with documented assessment demonstrating insufficient response to these, or unacceptable Adverse Drug Effects (ADEs).<sup>3-5, 8-10</sup>

## **PRESCRIBING AND DISPENSING**

- ClopineCentral™ is the monitoring system administered by Pfizer Australia Pty Ltd. It requires all patients, prescribing doctors, dispensing pharmacists, Centre Co-ordinators and registered centres using clozapine (Clopine®) to be registered with the database. Pharmacist registration is centre-specific and pharmacists working in PCH dispensary should be registered. Registration of prescribers is also site-specific.<sup>6</sup>

It is the prescribing doctor's responsibility to ensure that each patient for whom he/she prescribes clozapine is monitored in accordance with the requirements of the ClopineCentral™ protocol.<sup>6</sup>

## **CONTRAINDICATIONS**

- Hypersensitivity to clozapine or any components of the formulation.<sup>2-4, 9,11</sup>
- Central nervous system (CNS) depression from any cause.<sup>2-4, 9,11</sup>
- Alcoholic and toxic psychosis.<sup>3, 9,11</sup>
- Paralytic ileus.<sup>2-4, 9,11</sup>
- Severe cardiac disease or circulatory collapse.<sup>2-4, 9,11</sup>
- Bone marrow disorders, drug-induced (including clozapine-induced) neutropenia or agranulocytosis.<sup>2-4, 9,11</sup>
- Uncontrolled epilepsy.<sup>3, 9,11</sup>
- Severe renal impairment.<sup>2-4, 9,11</sup>
- Severe hepatic impairment.<sup>2-4, 9,11</sup>
- Patients unable to undergo regular blood tests.<sup>9,11</sup>

## WARNING AND PRECAUTIONS

### Special Warnings and Precautions:

**Clozapine Induced Gastrointestinal Hypomotility:** Severe gastrointestinal adverse reactions have occurred with the use of clozapine resulting in potential outcomes of hospitalisation, surgery and death. Prior to initiating and during treatment with clozapine, screen for constipation and if necessary, manage as per current clinical guidelines.<sup>9,11</sup>

**Myocarditis/cardiomyopathy:** Cases of myocarditis, some of which have been fatal, and cardiomyopathy have been reported in patients on clozapine. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be stopped, and the patient immediately referred to a cardiologist. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with clozapine.<sup>9,11</sup>

**Agranulocytosis:** Clozapine can cause agranulocytosis. Its use should be limited to people with schizophrenia: who are non-responsive to, or intolerant of other antipsychotic drugs; who have initially normal leucocyte findings; and in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) [weekly during the first 18 weeks, at least monthly thereafter throughout treatment, and for 1 month after complete discontinuation of clozapine] can be performed.<sup>9,11</sup> (see Sections on Monitoring and Adverse Effects for details)

### Other precautions:

- Tobacco smoking – increases clearance of clozapine (dose may need to be adjusted by up to 50%).<sup>2, 4, 9, 11</sup>
- Medications that may cause agranulocytosis; neutropenia seems to be more common in children and adolescents.<sup>2,4, 9, 11</sup>
- Respiratory failure – may cause respiratory depression or worsen that associated with, e.g., alcohol, benzodiazepines.<sup>2, 9, 11</sup>
- Hyperthyroidism – increases risk of acute dystonia.<sup>2</sup>
- Temperature regulation – may result in hypo or hyperthermia in conditions such as extreme heat or cold, with exercise, or with use of other drugs that affect temperature regulation, e.g., anticholinergics, topiramate. If high fever present, consider possibility of neuroleptic malignant syndrome.<sup>2, 4, 9, 11</sup>
- Shock – drug-related hypotension may worsen symptoms.<sup>2, 9, 11</sup>
- Gastrointestinal obstruction, bladder outlet obstruction, urinary retention, myasthenia gravis – may be exacerbated by the anticholinergic effects of clozapine.<sup>4, 9, 11</sup>
- Risk factors for angle-closure glaucoma – acute angle-closure crisis may rarely be precipitated.<sup>2, 4, 9, 11</sup>
- Low WBC count or previous blood dyscrasia – may increase risk of clinically significant dyscrasia.<sup>9, 11</sup>

- Diabetes – clozapine can increase blood glucose.<sup>4, 9, 11</sup>
- Neurological precautions in patients with:
  - Parkinson's disease
  - Lewy body dementia
  - Epilepsy or those at seizure risk <sup>4, 9, 11</sup>
- Cardiovascular precautions in patients with:
  - Prolonged QT interval
  - Orthostatic hypotension
  - Venous thromboembolism (VTE) <sup>4, 9, 11</sup>
- Sleep apnoea – use clozapine with caution especially if patient on other CNS depressants.<sup>9, 11</sup>
- Surgery precautions:
  - Reduced doses of anaesthetics and CNS depressants may be necessary. <sup>2, 9, 11</sup>
- Hepatic Impairment – consider dose reduction.<sup>4, 9, 11</sup>
- Pregnancy – Category C; use only when the benefits outweigh the risks.<sup>9, 11</sup>

## FORMULATIONS

Listed below are products available at PCH, other formulations may be available, check with pharmacy if required:

- Clozapine (Clopine® Brand) 25 mg, 50 mg, 100 mg, 200 mg tablets
- Clozapine (Clopine® Brand) 50 mg/mL oral suspension 100 mL – currently out of stock until 2024-2025
- Clozapine (Versacloz® Brand) 50 mg/mL oral suspension 100 mL

(Versacloz® is an unregistered product approved for supply under Section 19A of the Therapeutic Goods Act due to a shortage of Clopine® suspension 50 mg/mL expected until Jan 2025)<sup>1, 9</sup>

*It is important that once a patient is commenced on a specific brand of clozapine, they continue this brand as each has a separate monitoring service and information is not transferrable across systems.*

## DOSAGE & DOSAGE ADJUSTMENTS

### Oral dosing:

**Starting Therapy:** 12.5 mg once or twice daily on the first day, followed by increases of 12.5 - 25 mg every 3-5 days if tolerated and required, up to 200-300 mg daily within 2-3 weeks.<sup>2-5, 9, 11</sup>

**Maintenance Dosage:** After achieving a maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is recommended to the level of 150-300 mg/day given in divided doses. If the daily dose does not exceed 200 mg, a single administration in the evening may be appropriate.<sup>2-4, 9, 11</sup>

**Maximum Dosage:** Although some children may respond satisfactorily to lower doses, further increases may be needed to a maximum of 450 mg.<sup>2-4, 9, 11</sup>

- The usual adult maximum dose is 600 mg/day. However, a few patients may require larger doses to obtain maximum therapeutic benefit, in which case judicious increments (i.e., not exceeding 100 mg per week) are permissible up to a maximum of 900 mg/day. The possibility of increased adverse effects occurring at doses over 450 mg/day must be borne in mind.<sup>9,11</sup>
- **Doses up to 200 mg are usually given as a single dose in the evening. Larger doses may need to be divided with the large portion at bedtime to minimise adverse effects.**<sup>2,9, 11</sup>

### Dosing Adjustments:

#### **Renal impairment:**

- Consider dosage reduction.<sup>2, 9, 11</sup>

#### **Hepatic impairment:**

- Consider dosage reduction.<sup>2, 9, 11</sup>

**Restarting therapy:** In patients in whom the interval since the last dose of clozapine exceeds 48 hours, treatment should be re-instated with 12.5 mg given once or twice daily on the first day. If this dose is tolerated it may be feasible to titrate the dose to the therapeutic level.<sup>3, 9, 11</sup>

**Discontinuation of therapy:** The dosage should be gradually reduced over a period of **1-2 weeks minimum** if termination of therapy is not due to neutropenia. This is important to avoid withdrawal symptoms and minimise the chance of relapse.<sup>5, 9,11</sup>

## **ADMINISTRATION**

**Oral tablets:** Swallow clozapine tablets with water or other liquids.<sup>9,11</sup>

**Clozapine suspension:** See specific instructions for use depending on brand available.

- Clozapine suspension must be administered by healthcare professionals who are staff at centres registered with the clozapine monitoring and support network, ClopineCentral™.<sup>9, 11</sup>
- Do not mix clozapine suspension with any other beverages as this may change the properties of the active drug.<sup>2, 9, 11</sup>

**Where a dose is required urgently, tablets can be crushed. A mask and gloves must be worn when crushing tablets.**

**Clozapine (Clopine® brand) oral suspension 50 mg/mL****24 hours before the first use.**

1. Open the bottle and push the bottle adaptor into the top of the bottle. Leave the bottle adaptor in place on the bottle.
2. To ensure the suspension is dispersed, before dispensing the first dose only, shake the bottle for a period of 90 seconds. This is important to ensure any sedimentation that may have occurred during storage has been resuspended.
3. Note the expiry date on the product label in permanent marker as ninety (90) days from the date of first opening.<sup>9,11</sup>
4. Leave the bottle of suspension to stand for 24 hours before dispensing the first dose to allow dissipation of air bubbles formed during shaking.<sup>9, 11</sup>

All doses should be measured using an appropriate purple enteral syringe.<sup>9, 11</sup>

**Immediately before dispensing doses**

1. Immediately before each dose, the bottle should be further shaken for 10 seconds to ensure the suspension is homogeneous.
2. Turn the bottle of clozapine suspension upside down and slowly draw the prescribed dose of liquid into the oral dispenser using the graduations displayed in millilitres.
3. Turn the bottle upright and detach the oral dispenser from the bottle adaptor. Invert the oral dispenser to prevent spillage.<sup>9,11</sup>
4. Administer the clozapine suspension directly from the oral dispenser undiluted or if dilution is required add the suspension to a cup with some water ONLY. Stir and drink the entire mixture right away.<sup>9, 11</sup>

Do not mix Clozapine suspension with any other beverages as this may change the properties of the active drug.<sup>2, 9, 11</sup>

Clozapine (Clopine ® brand) suspension can be used for up to 90 days following the first opening.

**Clozapine (Versacloz ® brand) suspension 50 mg/mL**

VERSACLOZ Oral Suspension is administered by the oral syringes provided (1 mL or 9 mL).

If the dose is 1 ml (50 mg) or less, use the 1 mL syringe.

For doses over 50 mg, use the larger 9 mL syringe.

1. Shake the bottle for 10 seconds prior to each use, press the syringe adaptor into the top of the bottle.
2. Fill the oral syringe (1 mL or 9 mL) with air and insert into the adaptor. Dispel air into the bottle and then turn the bottle upside down.
3. Draw out the prescribed amount of the suspension from the bottle and administer the medication immediately.
4. Close the bottle with the same cap without removing the bottle adaptor.

Versacloz® suspension can be used for up to 100 days following the first opening.<sup>12</sup>

## MONITORING

Development of granulocytopenia and agranulocytosis is a risk inherent to clozapine therapy. Although generally reversible on withdrawal of the drug, agranulocytosis can prove fatal. Most cases occur within the first 18 weeks of treatment. Because immediate withdrawal of the drug is required to prevent the development of life threatening agranulocytosis, monitoring of WBC is mandatory.<sup>9, 11</sup>

**All patients receiving treatment with clozapine require regular blood tests to monitor white blood cell (WBC) counts and neutrophils. This must be performed before commencing therapy, regularly during therapy and after ceasing treatment.**

**NOTE: In accordance with the requirements of the ClopineCentral™ protocol ALL blood test results must be recorded in the ClopineCentral™ online platform.**

A [Clozapine Initiation and Titration Chart](#) must be used for all new patients started on clozapine.

See [Guidelines for the use of the WA Clozapine Initiation and Titration Chart](#) and [Guidelines for the Safe and Quality Use of Clozapine Therapy in the WA health system](#).

Medical supervision and resuscitation facilities must be available when initiating treatment because of possible orthostatic hypotension with respiratory or cardiac failure.<sup>2,9, 11</sup>

### Before Starting Clozapine (Baseline measurements)

- White blood cell (WBC) count and full blood count (FBC) must be performed **within 10 days prior to initiation**.<sup>9, 11</sup>
- Patients must have:
  - WBC counts  $>3.5 \times 10^9/L$
  - Absolute neutrophil counts (ANC)  $>2 \times 10^9/L$
  - Normal FBC<sup>9, 11, 13</sup>
- A completed blood test to identify blood group (for registration with ClopineCentral)<sup>14</sup>
- Other Monitoring:<sup>9,11,13,14</sup>
  - Liver function tests (LFTs)
  - Urea and electrolytes (U & Es)
  - Fasting plasma glucose
  - Fasting lipids
  - Troponin – within 10 days of starting clozapine
  - C-reactive protein (CRP) – within 10 days of starting clozapine
  - Electrocardiogram (ECG) (QT interval)
  - Cardiac echocardiogram
  - Beta human chorionic gonadotropin (HCG) (female)
  - Weight, height, waist circumference and body mass index (BMI)
  - Bowel function and constipation monitoring
  - Full physical examination (including temperature, pulse, respiration rate, lying and standing blood pressure)
  - Dietitian review
  - Record smoking status.



## After Starting Clozapine

- WBC count and ANC and FBC (including eosinophils) must be monitored weekly for the first 18 weeks.<sup>9, 11</sup>
- An immediate FBC must be performed if any symptoms or signs of infection occur.<sup>9, 11</sup>
- Following the first 18 weeks of treatment, the WBC, ANC and FBC must be performed at least monthly throughout treatment and for ONE month after complete discontinuation of clozapine.<sup>9, 11</sup>
- Other Monitoring:<sup>9,11,13,14</sup>
  - Liver function tests (LFTs) – 6 monthly
  - Urea and electrolytes (U & Es) – 6 monthly
  - Fasting plasma glucose – at 3 months, 6 months, then 6 monthly
  - Fasting lipids – at 3 months, 6 months, then 6 monthly
  - Troponin – weekly for the first 4 weeks, then when necessary
  - C-reactive protein (CRP) – weekly for the first 4 weeks, then when necessary
  - ECG (QT interval) – weekly for the first 4 weeks, then when necessary
  - Cardiac echocardiogram – at 3 months and then at 1, 2, 5 years
  - Beta HCG – when necessary
  - Weight, height, waist circumference and BMI – weekly for first 18 weeks then monthly
  - Constipation monitoring – daily bowel chart for 4 weeks (check bowel habits weekly for inpatients, check bowel habits at every outpatient review)
  - Full Physical examination - annually
  - Dietitian review – annually
  - Smoking status check

## Interruption to therapy (for non-haematological reason)

If the patient's current monitoring period is weekly and treatment is interrupted for more than 72 hours but less than 4 weeks.<sup>9, 11</sup>

- Monitor WBC and ANC weekly for at least 6 weeks or for as long as necessary to achieve a total of 18 weeks of weekly monitoring.<sup>9, 11</sup>
- If no haematological abnormality at 18 weeks resume regular monthly monitoring.<sup>9, 11</sup>

If the patient's current monitoring period is monthly and treatment is interrupted for more than 72 hours but less than 4 weeks.<sup>9, 10</sup>

- Monitor WBC and ANC weekly for 6 weeks then continue with monthly monitoring if no problems detected.<sup>9, 11</sup>

If clozapine treatment has been interrupted for 4 or more weeks.<sup>9, 11</sup>

- Recommence as for a new patient with weekly monitoring for the next 18 weeks.<sup>9, 11</sup>

## Further monitoring

- If infection occurs or WBC count drops below  $3.5 \times 10^9/L$  or a substantial drop from baseline:<sup>9, 11</sup>
  - A repeat WBC and FBC should be performed. If results confirm a  $WBC < 3.5 \times 10^9/L$  and/or ANC between  $1.5 \times 10^9/L$  to  $2 \times 10^9/L$  counts must be checked at least twice weekly.<sup>9, 11</sup>



- If the WBC count falls below  $3.0 \times 10^9/L$  and/or the ANC drops below  $1.5 \times 10^9/L$ :<sup>9, 11</sup>
  - **Clozapine therapy must be withdrawn at once** and the patient should be closely monitored.<sup>9, 11</sup>
  - WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.<sup>9, 11</sup>
- Following discontinuation of clozapine, haematological evaluation must be continued until haematological recovery has occurred.<sup>9, 11</sup>
- If clozapine therapy has been withdrawn and a further fall of WBC count below  $2 \times 10^9/L$  occurs and/or the neutrophil granulocytes decrease below  $1 \times 10^9/L$ :<sup>9, 11</sup>
  - Referral to an experienced haematologist is required.<sup>9, 11</sup>

**Patients in whom clozapine therapy has been discontinued as a result of white blood cell deficiencies must not be re-exposed to clozapine.**<sup>9, 11</sup>

**Table 1: Clozapine Monitoring Schedule**

| Clozapine Blood Results Monitoring System |   | Recommended Action  |
|---|---|---|
| <b>Green Range</b>                        | WBC greater than $3.5 \times 10^9/L$ AND Neutrophils greater than $2.0 \times 10^9/L$ | Continue clozapine therapy  |
| <b>Amber Range</b>                        | WBC $3.0 - 3.5 \times 10^9/L$ AND/OR Neutrophils $1.5 - 2.0 \times 10^9/L$            | Continue clozapine therapy with twice-weekly blood tests until return to "green" range    |
| <b>Red Range</b>                          | WBC less than $3.0 \times 10^9/L$ AND/OR Neutrophils less than $1.5 \times 10^9/L$    | Stop clozapine therapy immediately. Contact haematologist and Clozapine Monitoring Centre |

#### **Myocarditis monitoring** (see [Monitoring Clozapine-induced Myocarditis](#))

- Myocarditis is inflammation of heart muscle that can lead to cardiomyopathy.
- It is a rare side effect of clozapine therapy which tends to occur in the first month of starting treatment.
- Clinical findings may include increased CRP, increased troponin, and eosinophilia.<sup>14</sup> Symptoms include tachycardia at rest accompanied by other signs and symptoms of heart failure or arrhythmias. Fatigue, flu-like symptoms, chest pain or fever that is otherwise unexplained may also be present.
- If myocarditis or cardiomyopathy is suspected, urgent cardiologist referral is required, and clozapine should be stopped.
- If cardiomyopathy is diagnosed, clozapine should be discontinued unless the benefit clearly outweighs the risk to the patient.
- Patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with clozapine unless the benefit outweighs the risk.<sup>9,11</sup>

#### **Gastrointestinal (GI) hypomotility monitoring**

- Clozapine may cause severe GI adverse reactions ranging from nausea, vomiting, overflow diarrhoea, constipation, to paralytic ileus, intestinal impaction and more severe complications.

- Screen for constipation before starting clozapine and throughout treatment and treat, as necessary.
- Monitor for changes in the frequency or character of bowel movements.
- Monitor for signs and symptoms of complications of hypomotility (e.g., nausea, vomiting, abdominal distension or pain, nil urge to defecate, constipation, inability to defecate).
- If constipation or gastrointestinal hypomotility are identified, monitor, and treat promptly, as per current clinical guidelines to prevent severe complications.<sup>9,11</sup>

## ADVERSE EFFECTS

### Children and adolescents are at greater risk for:

- Acute dystonic reactions. Children may not complain of akathisia in the same way as adults; monitor closely.<sup>2, 4, 9, 11</sup>
- Weight gain, metabolic abnormalities and hyperprolactinaemia.<sup>2, 4, 9, 11</sup>
- Possible effects on fertility (inhibits spermatogenesis in animal studies).<sup>11</sup>

**Common:** drowsiness (occurs in 40%), hyper-salivation (can cause aspiration pneumonia), constipation (may result in obstruction, paralytic ileus, and death), seizures, headache, tachycardia, hyperpyrexia (5%), hepatitis, neutropenia, vomiting, urinary incontinence, nocturnal enuresis.<sup>2, 4, 9, 11, 15</sup>

**Infrequent:** myocarditis (usually in the first month of initial treatment but rarely may occur when starting after a break in treatment), agranulocytosis, eosinophilia, priapism, extrapyramidal side effects (EPSE).<sup>2, 4, 9, 11, 152, 4, 9, 11, 14</sup>

**Rare:** cardiomyopathy, hypertension, myoclonic jerks, interstitial nephritis, respiratory arrest, fulminant hepatic necrosis, polyserositis.<sup>2, 4, 9, 11, 152, 4, 9, 11, 14</sup>

**Clozapine can impair cognition and therefore affect learning at school.**<sup>11</sup>

## STORAGE

### Tablets

- Store below 30°C in a cool dry place.
- Protect from light.

### Suspension

- Store below 25°C. Protect from Light.
- Clopine® brand - may be used for up to 90 days after first opening.
- Veracloz® brand - may be used for up to 100 days after first opening.
- Recap the bottle tightly following each use.

## INTERACTIONS

Clozapine may interact with other medications; consult PCH approved references (e.g. [Clinical Pharmacology](#)), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

Specific **pharmacokinetic-related** interactions include but are not restricted to:

- Competition for protein binding sites (e.g., warfarin and digoxin).<sup>9,11</sup>
- Interactions with medications that effect cytochrome P450 isoenzymes, in particular CYP1A2, CYP2D6 and CYP3A4. Examples include SSRIs (fluoxetine, paroxetine, sertraline [up to twofold increase in clozapine levels], fluvoxamine [up to tenfold increase in clozapine levels] or citalopram), venlafaxine and carbamazepine.<sup>9,11</sup>

Specific **pharmacodynamic-related** interactions include but are not restricted to:

- Medications known to have a substantial potential to depress bone marrow.<sup>9,11</sup>
- Medications that contribute to CNS depression. Examples include benzodiazepines and antipsychotics.<sup>9,11</sup>
- Medicines known to affect the corrected QT (QTc) interval, or those that can cause electrolyte imbalances.<sup>9,11</sup>
- Concomitant use of lithium or other CNS-active agents may increase the risk of developing neuroleptic malignant syndrome.<sup>9,11</sup>
- Medications with anticholinergic, hypotensive or respiratory depressant effects (e.g., promethazine).<sup>9,11</sup>

**NOTE: Due to the extremely high prevalence of interactions, all proposed medication changes and additions should be thoroughly screened for medication interactions.**

## ADDITIONAL CONSIDERATIONS

- Adequate contraceptive measures must be ensured in women of childbearing potential.
- Clozapine levels may be lower in patients that smoke. Smokers may require up to twice the daily dose of non-smokers to obtain an equivalent clozapine concentration. Smoking cessation may cause toxicity in a patient stabilised on clozapine. Monitor changes in smoking patterns. Consider baseline serum clozapine levels and/or empiric dosage adjustments (30-40% reduction) in patients expected to have a prolonged hospital stay with forced smoking cessation. Symptoms from increasing clozapine may develop 2-4 weeks after smoking cessation.<sup>4, 5</sup>
- Patients should be advised to minimise caffeine intake during therapy with clozapine as it may inhibit its metabolism via CYP1A2 and potentially reduce its clearance by roughly 15%.<sup>4</sup>
- Avoid the concomitant use of long acting depot antipsychotics due to the inability of these to be rapidly removed from the body in situations where this may be required, e.g. granulocytopenia.<sup>9, 11</sup>

- At each consultation, the patient should be reminded to contact the treating doctor immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.<sup>9, 11</sup>

## DISPENSING

- Patients will only be supplied with clozapine once a valid blood test has been entered into ClopineCentral™.
- The WBC and neutrophil count recorded must not be more than 48 hours old.
- Patients will only be supplied with a sufficient quantity of clozapine until their next scheduled blood test, or a lesser quantity if required by the patient's usual treating psychiatrist.
- Discharge prescriptions will not be dispensed in the absence of a validated ClopineCentral™ blood test entry.
- Prescriptions should be accompanied by a Clopine® Blood Count Record Form.

*\*\*Please note: The information contained in this guideline is to assist with the preparation and administration of **Clozapine**. Any variations to the doses recommended should be clarified with the prescriber prior to administration\*\**

## Related CAHS internal policies, procedures, and guidelines

[Psychotropic Medication: Physical Health Monitoring Handbook CAMHS](#)

[CAMHS Psychotropic Medication – Monitoring Adverse Physical Health Effects Policy](#)

[Off-Label Psychotropic Prescribing Guide for CAMHS Clinicians](#)

[Consent for Medication Use](#)

[High Risk Medicines Policy](#)

Standard Operating Procedure for Clozapine Dispensing (located in Pharmacy Department SharePoint)

Out of Hours Supply of Clozapine (located in Pharmacy Department SharePoint)

## Related external legislation, policies, and guidelines

[Guidelines for the use of the WA Clozapine Initiation and Titration Chart](#)




[Clozapine Initiation and Titration Chart](#)

[Guidelines for the Safe and Quality Use of Clozapine Therapy in the WA health system](#)

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