

# SESLHD PROCEDURE COVER SHEET



**Health**  
South Eastern Sydney  
Local Health District

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<b>KEY TERMS</b>	Clozapine, Prescribing, Administration, Monitoring
<b>SUMMARY</b>	The document describes the policy and procedure for prescribing, administration and monitoring of Clozapine in SESLHD

## **COMPLIANCE WITH THIS DOCUMENT IS MANDATORY**

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**1. POLICY STATEMENT**

The purpose of this document is to ensure that Clozapine is safely and appropriately prescribed, dispensed, administered and monitored. The procedure is intended to be used in all situations where treatment with Clozapine is used. The procedure should be read in conjunction with the approved Product Information,<sup>14</sup> the Clozapine Central Clozapine Manual,<sup>14</sup> and the [NSW Ministry of Health Policy Directive PD2012\\_005 - Clozapine-induced Myocarditis - Monitoring Protocol](#).<sup>1</sup>

Gaining a better understanding of the potential risks associated with Clozapine will enable SESLHD staff to ensure that appropriate protocols and guidelines for the effective monitoring and management of patients taking Clozapine are in place.

**2. BACKGROUND**

Clozapine is an antipsychotic medication which may be effective in treatment-resistant schizophrenia, or where other antipsychotics have not been tolerated (extrapyramidal side effects, tardive dyskinesia etc).

Due to potentially life-threatening side effects of this medication, patients receiving Clozapine must be monitored carefully throughout their treatment, both during admission and after discharge (by the outpatient Clozapine Clinics located across the SESLHD, and Clozapine-registered GPs where available). The document sets out clinical and administrative procedures for safe and effective prescribing, administration and monitoring of Clozapine.

**3. RESPONSIBILITIES**

Please refer to [SESLHD Mental Health Service Business Rule SESLHDBR/072 - Clozapine Roles and Responsibilities within the South Eastern Sydney Local Health District Mental Health Service](#)

**4. DEFINITIONS**

Definition of NHMRC grades of recommendations:

Grade of Recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

“Off label” prescribing:

“Off label” prescribing occurs when a drug is prescribed for an indication, route of administration, or patient group that is not included in the approved product information document for that drug.

### Abbreviations:

POWH: Prince of Wales Hospital  
TSH: The Sutherland Hospital  
STGH: St George Hospital  
KBIM: Keeping Body In Mind  
MH: Mental Health

NIMC: National Inpatient Medication Chart  
eMEDS: Electronic Medication Management System approved for use in  
SESLHD  
eMR: Electronic Medical Record

IMMS: Incident Information Management System

S100: Section 100 (Highly Specialised Drugs Program)  
CMI: Consumer Medicines Information Leaflet

FBC: Full Blood Count  
WCC: White Cell Count  
EUC: Electrolytes, Urea, Creatinine  
LFTs: Liver Function Tests  
CRP: C-Reactive Protein  
HbA1c: Glycated Haemoglobin  
ECG: Electrocardiogram  
BMI: Body Mass Index  
ULN: Upper Limit of Normal  
BPM: Beats Per Minute  
NMS: Neuroleptic Malignant Syndrome

### 5 PROCEDURE

#### 5.1 Indication for Clozapine

Clozapine is indicated for patients with treatment resistant schizophrenia who have been non-responsive to, or intolerant of, other antipsychotic drugs.<sup>14</sup>

Non-responsiveness is defined as an inadequate response to at least two other antipsychotic drugs.<sup>14</sup> Adequate compliance should be ensured.

Intolerance is defined as the inability to achieve adequate benefit with other antipsychotic drugs because of severe and untreatable neurological adverse effects (extrapyramidal side effects, tardive dyskinesia or tardive dystonia).<sup>14</sup>

Clozapine is occasionally used “off label” for other indications such as treatment resistant mania and psychosis associated with Parkinson’s or Huntington’s diseases.<sup>8</sup> [The SESLHD Policy SESLHDPD/182 - Off-label use of registered medicines and use of unlicensed medicines](#)<sup>2</sup> should be followed.

#### 5.2 Contraindications<sup>14</sup>

- History of drug induced granulocytopenia / agranulocytosis
- Bone marrow disorders
  - Clozapine Haematologist may be contacted for advice
- Circulatory collapse and / or CNS depression due to any cause
- Alcoholic and other toxic psychoses; drug intoxication; comatose conditions
- Severe renal, hepatic or cardiac disease (eg; myocarditis)
  - Seek specialist advice
- Uncontrolled epilepsy
- Paralytic ileus.

#### 5.3 INITIATION OF TREATMENT

See Clozapine Registration Check List (Document 6.1) for a summary.

##### 5.3.1 Patient Information

Prior to initiation of Clozapine, the Medical Officer should discuss the risks and benefits of Clozapine treatment with the patient, particularly in comparison with alternative treatments.

The discussion should, where possible, include the following:

- Reason for regular blood tests and the necessity for compliance with these, i.e. an explanation of **agranulocytosis / neutropenia**, its consequences and how this may

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affect physical health. Advice should be given to contact the treating Medical Officer or Local Medical Officer immediately if signs of infection, fever, sore throat, mouth ulcers or flu-like symptoms develop.

- The need for physical observation monitoring.
- The role of ClopineCentral and their need to record limited personal data about the patient.
- How current medication will be withdrawn or adjusted.
- Common side effects (See APPENDIX 1).<sup>9 p4, 14, 16 p165-166</sup>
- Potential medical complications, especially cardiac complications. Inform patient of symptoms of **myocarditis**, and advise to inform Nurse or Medical Officer (inpatients), or present to the Emergency Department (outpatients) if unwell.
- The risk of **constipation**, and the importance of informing their Medical Officer promptly if this occurs. Recommend a high fibre diet and plenty of fluids.<sup>16 p177, 27</sup>
- Diet and exercise advice regarding possible weight gain and metabolic side effects.
- The consequences of poor adherence with treatment.
- Enquire about smoking status (current smoker or recently quit). Discuss the impact of quitting or reducing smoking on Clozapine levels (i.e. reduced metabolism of the drug).<sup>3, 4, 16 p 688, 18</sup>

A record of this discussion and the points covered should be recorded in the patient's medical notes.

If the patient does not have capacity to understand the information or provide consent, this should be documented clearly in the patient notes.

The primary carer or next of kin should ideally be consulted regarding the decision where available.

The patient should be provided with a Consumer Medicine Information (CMI) leaflet.<sup>19</sup>

The patient should read the Clopine (Clozapine) Monitoring System Privacy Statement, and sign the Clopine Patient Consent Form.<sup>20</sup>

- This should be countersigned by the Medical Officer.
- If the patient is unable to provide informed consent, this should also be documented on the form.
- The form should be filed in the patient notes.

**5.3.2 Pre-treatment Tests**<sup>1, 9,10,15</sup>

Prior to initiation of Clozapine, the following tests should be performed, and reviewed by the treating clinicians:-

- Blood group\*
- Baseline:
  - FBC (performed within 10 days of the intended start date)\*
  - EUC
  - LFTs
  - CRP
  - Troponin I or T
  - Fasting Blood Glucose Level or HbA1c
  - Fasting Lipids (Total Cholesterol, HDL, LDL, Triglycerides)
  - Weight, Height, BMI, Waist circumference (Metabolic Monitoring Form completed)
  - BP
  - Pulse Rate
  - Temperature
  - Respiration Rate
  - Full Physical Exam
  - ECG
  - Echocardiogram (recommended)<sup>1</sup>

\* Essential for patient registration with ClopineCentral

Personal and family history of cardiac, metabolic and lifestyle risks should be assessed.

The Metabolic Monitoring Form should be completed on EMR by the treating team.

**Interpretation of pre-treatment blood count:**<sup>15 p12</sup>

Status	WCC and Neutrophil Result	Action
Green range	WCC > 3.5 x 10 <sup>9</sup> /L AND Neutrophils > 2 x 10 <sup>9</sup> /L	Clozapine may be commenced following successful registration
Amber range	WCC 3.0 - 3.5 x 10 <sup>9</sup> /L AND / OR Neutrophils 1.5 - 2.0 x 10 <sup>9</sup> /L	Wait one week and repeat blood count. If results are still in this range, Clozapine <u>may</u> be commenced under the supervision of the Medical Officer
Red range	WCC < 3.0 x 10 <sup>9</sup> /L AND / OR Neutrophils < 1.5 x 10 <sup>9</sup> /L	Consult Clopine Haematologist for advice



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**5.3.3 Registration with a Clozapine Monitoring Service**

- Due to the risk of neutropenia and fatal agranulocytosis, all patients must be registered with a Clozapine monitoring service provided by the manufacturer.<sup>15</sup> SESLHD currently uses the Clopine brand which requires patients to be enrolled with the ClopineCentral patient monitoring service.
- All Medical Officers prescribing Clozapine, and pharmacists dispensing Clozapine must also be enrolled with ClopineCentral at POWH / STGH / TSH (registration is site specific).<sup>15</sup> Registration forms are available from the Clozapine coordinator or ward pharmacist.
- The Medical Officer must register the patient with ClopineCentral (by providing a completed “Registration of New Patients” form<sup>15 p28</sup> to the Clozapine coordinator or ward pharmacist). If unavailable, the form may be faxed directly to ClopineCentral.
- The Clozapine Registration Checklist (Document 6.1) should be followed and provided to the Clozapine coordinator or ward pharmacist.
- ClopineCentral will provide confirmation of patient registration to the treating medical officer, Clozapine coordinator, and pharmacist coordinator via email.
- The patient will be issued with a Clopine Patient Number (CPN), which must be recorded in the patients’ notes, and should be used in all subsequent correspondence with ClopineCentral.<sup>15</sup>
- Note that for privacy reasons, ClopineCentral do not keep on record the patient’s name. The patient identifiers provided to ClopineCentral are the patient’s initials, date of birth, blood group, gender and Clopine Centre.
- **Confirmation that the patient is registered with ClopineCentral must be obtained before prescribing Clozapine.**<sup>15</sup>

**5.3.4 Medication Review**

- A review of the patient’s existing medication must take place:
- A clear plan should be in place regarding the withdrawal of previous antipsychotics.
  - If patients are taking another antipsychotic drug when they start Clozapine, this can be rapidly phased out as the Clozapine is increased, generally by the time the dose is up to 100mg/day.<sup>8</sup> Consider potential additive side effects, such as hypotension, sedation, effect on QTc interval, anticholinergic effects).
- Drugs known to have a substantial potential to depress bone marrow function (eg; carbamazepine, phenothiazines) should not be used concurrently with Clozapine<sup>14</sup>
- Concomitant use of long-acting depot antipsychotics should be avoided where possible because of the inability of these medications, which may have the potential to be myelosuppressive, to be rapidly removed from the body in situations where this may be required, eg; granulocytopenia<sup>14</sup>
- Benzodiazepines should be used sparingly with caution, as patients may have an increased risk of circulatory collapse, which on rare occasions may be profound.<sup>8,14</sup>
- Common drug interactions are summarised in APPENDIX 2.<sup>21</sup> Further information on drug interactions may be obtained from the Clopine Product Information<sup>14</sup>, available via MIMS Online, or by contacting the hospital’s pharmacy department.

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**5.3.5 Dosing Schedule**

- Clozapine should be commenced at a low dose, increasing slowly as tolerated and according to patient response. Adverse effects such as sedation, postural hypotension, and hypersalivation are often dose-dependent and associated with rapid titration.<sup>16 p147</sup>
- The recommended starting dose of Clozapine is 12.5 mg in the morning on the first day, followed by 25 mg on the second day.<sup>9</sup>
- The first dose must be given early in the day to allow for six hours of post-dose physical observation monitoring (see Section 5.5.1).
- If well tolerated, the daily dose may then be increased slowly in increments of 25mg to a dose of up to 200 – 300mg / day, or lower if side effects occur.<sup>8,14,16 p147, 24</sup> This can usually be achieved in two – three weeks.<sup>14,16</sup>
- The total daily dose may be divided unevenly, with the larger portion given at night.<sup>14</sup> Once daily dosing at night may decrease daytime sedation and improve compliance.<sup>8</sup>
- A suggested dosing schedule is provided below:<sup>9, 22</sup>

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
AM	12.5 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
PM	X	X	X	25 mg	25 mg	50 mg	75 mg	100 mg	100 mg	100 mg	125 mg	125 mg	125 mg	150 mg

- Once the target dose is reached, the patient’s clinical response should be monitored for at least two weeks before a further increase.<sup>23</sup>
- Clozapine levels may be measured after the patient has achieved a steady-state concentration on a stable dose for at least one week<sup>24</sup> (See Section 5.5.4).
- Further dosage increases may be made slowly if required, in increments of 50 to 100 mg each week.<sup>14, 16</sup>
- In most patients, antipsychotic efficacy can be expected with 200mg to 450 mg per day, however some patients respond to lower doses. The lowest effective dose should be used.<sup>14</sup>
- Lower doses are required for elderly and female patients, and in those prescribed certain CYP enzyme inhibitors. Smokers may require higher doses.<sup>16 p147-9</sup>
- The plasma level threshold for therapeutic response has been variously reported from 200 to 550 microg/L,<sup>16p4, 21</sup> with most studies indicating that response occurs in the range 350-420microg/L. Response may occur at lower levels.<sup>16p148-149</sup>
- In those not responding to Clozapine treatment, the dose may be adjusted to give plasma levels in the range 350 – 500microg/L to ensure an adequate trial.<sup>16 p5</sup>
- An upper limit of the target plasma level range has not been defined. A “therapeutic” upper limit of 600-800microg/L has been proposed, however placing an upper limit on the target range may discourage potentially worthwhile dose increases within the licensed dosage range.<sup>16 p5</sup>
- Manufacturers recommend a maximum dose of 600mg for most patients, with doses up to 900mg permissible<sup>14</sup>, although rarely needed.<sup>24</sup>
- A greater incidence of adverse effects may occur at doses over 450 mg/day,<sup>14</sup> or plasma levels above 900micrograms/L.<sup>11</sup>

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- Rapid dose increase, doses more than 600 mg per day and plasma concentrations above 1000 micrograms/L are associated with a higher incidence of seizures.<sup>24</sup>
- After achieving optimum therapeutic benefit, many patients can be managed effectively on lower doses. Careful downward titration is recommended.<sup>8, 15 p17</sup>
- Patients quitting or significantly reducing their level of tobacco smoking may need a reduction in dose, due to the reduced metabolism of Clozapine.
- N.B. Nicotine Replacement Therapy does not affect clozapine levels.
- Refer to NSW Ministry of Health Tools: <sup>3,4</sup>
  - [Tool03 - Clozapine and smoking cessation](#)
  - [Tool08 - Clozapine and consumers who resume or might resume smoking](#)

**5.3.6 Prescription, Supply and Administration of Doses**

- The National Inpatient Medication Chart (NIMC) or electronic Medication Administration Record (MAR) should be used for the prescription and administration of Clozapine, in accordance with [NSW Health Policy PD2013 043 Medication Handling in NSW Public Health Facilities](#)<sup>5</sup>, and local hospital procedures.
- The SESLHD / NSW Health Adult Clozapine Titration Chart<sup>9</sup> may be used where available, for the prescription and record of administration of Clozapine during the first 28 days of treatment, until a stable dose is reached.
- Clozapine is dispensed on a named-patient basis once the pharmacist has ensured that the patient is registered with ClopineCentral, and the FBC has been reviewed.
- If a dose is missed, the reason must be recorded on the chart using the NIMC or eMEDS non-administration codes,<sup>6</sup> and must also be documented in the patient's medical notes. A medical officer must be informed of the missed dose before the next dose is given.
- See Section 5.6 "Interruptions in therapy"
- N.B. If less than 48 hours of Clozapine have been missed, and the patient is on a titration schedule, Clozapine should be restarted at the dose prescribed before the event. <sup>16p148</sup>

**5.4 Adverse Effects**

See APPENDIX 1 for a table of common and important adverse effects of Clozapine, and suggested management options. <sup>9,14,16 p165-166</sup>

Further information about adverse effects may be obtained from the MIMS Clopine Product Information<sup>14</sup> available via CIAP, or by contacting the hospital's pharmacy department.

**5.5 Monitoring**

See Document 6.2 for a summary of monitoring requirements for inpatients.

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#### 5.5.1 Physical Observation Monitoring

##### Baseline – Before first dose:

Appropriate resuscitative facilities must be available.

The following parameters must be checked before the first dose of Clozapine:

- Blood Pressure (lying and standing)
- Pulse Rate
- Respiration Rate
- Temperature
- ECG
- Presence of constipation<sup>16p177</sup>

Medical Officer must be informed if:

- Blood pressure:
  - Systolic <100 or >180mmHg
  - Diastolic <60 or > 100mmHg
  - OR a postural drop of > 30mmHg
- Pulse Rate: < 50/min OR ≥ 120/min
- Temperature: < 35.5°C OR > 38.5°C
- Respiration Rate: < 10 OR > 25 breaths/min<sup>25 p15</sup>
- Patient is constipated<sup>16p177</sup>

Medical Officer should review ECG before commencement of Clozapine.

##### Day 1 – Post dose:

After the first dose, the following parameters must be monitored every half hour for two hours, then every hour for the next four (a total of six hours monitoring post-dose):<sup>10,22</sup>

- Blood Pressure (lying and standing)
- Pulse Rate
- Temperature
- Respiration Rate
- Signs or symptoms of:
  - Chest pain
  - Shortness of Breath
  - Sedation
  - Dizziness
  - Hypersalivation
  - Headache
  - Perspiration
  - Nausea
  - Enuresis
  - Infection

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The following parameters should then be monitored twice daily for at least four weeks whilst the patient is an inpatient, unless otherwise specified by the medical officer.

- Blood Pressure (lying and standing)
- Pulse Rate
- Temperature
- Respiration Rate
- Signs or symptoms of:
  - Chest pain
  - Shortness of Breath
  - Sedation
  - Dizziness
  - Hypersalivation
  - Headache
  - Perspiration
  - Nausea
  - Enuresis
  - Infection
  - Constipation<sup>9, 11,16p177</sup>

Observations should be taken pre-dose, and four-six hours post-dose (or pre- and post-dose if prescribed once daily at night.<sup>9,11</sup>

Physical observations (blood pressure, pulse rate, temperature and respiration rate) must be recorded on the Standard Adult General Observation Chart, or on the BTF Observation Chart on EMR, as per individual hospital procedure.

Clozapine Observation Charts are also used at POWH to record all observations (Documents 6.3.1 and 6.3.2).

Medical Officer must be informed if:

- Blood pressure:
  - Systolic <100 or >180mmHg
  - Diastolic <60 or > 100mmHg
  - OR a postural drop of > 30mmHg
- Pulse Rate: < 50 bpm OR ≥ 120 bpm, OR increased by > 30 bpm from baseline
- Temperature: < 35.5°C OR > 38.5°C
- Respiration Rate: < 10 OR > 25 breaths/min <sup>25 p15</sup>
- Chest pain
- Shortness of breath

If the patient has been refusing observations, this must be documented clearly in the notes, and the medical officer must be informed.

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Ongoing Observation Monitoring for Outpatients:

- Week 1, 2, 3, 4 – BP, Pulse Rate, Temperature, Respiration Rate <sup>1</sup>
- Week 6, 18 – BP <sup>1</sup>
- Then three monthly thereafter – BP, Pulse Rate, Temperature

See Document 6.4 for a summary of outpatient monitoring.

If the patient is discharged within the first two weeks of treatment, the Clozapine Consultant should be contacted for advice on additional monitoring and support requirements.

**5.5.2 Blood Count Monitoring**

Development of granulocytopenia and agranulocytosis may occur with Clozapine treatment. Although generally reversible on withdrawal of the drug, agranulocytosis can prove fatal. The majority of cases occur within the first 18 weeks of treatment (but it may occur at any time).

Because immediate withdrawal of the drug is required to prevent the development of life threatening agranulocytosis, monitoring of the WCC and neutrophil count is **mandatory**.<sup>14</sup>

WCC and Neutrophil counts must be monitored weekly for the first 18 weeks of treatment, and then every four weeks thereafter.<sup>15</sup>

Blood tests should be performed within 48 hours of dispensing Clozapine for outpatients.<sup>15</sup>

The ward pharmacist should ensure that FBC results are up to date before supplying Clozapine for inpatients.

Interpretation of FBC Results:<sup>15</sup>

Status	WCC & Neutrophil result	Action
Green range	WCC > 3.5 x 10 <sup>9</sup> /L AND Neutrophils > 2 x 10 <sup>9</sup> /L	Continue Clozapine therapy at usual monitoring frequency
Amber range	WCC 3.0 - 3.5 x 10 <sup>9</sup> /L AND / OR Neutrophils 1.5 - 2 x 10 <sup>9</sup> /L	Continue Clozapine with twice weekly blood tests (i.e. within four days of each other) until both counts return to 'green' range
Red range	WCC < 3.0 x 10 <sup>9</sup> /L AND / OR Neutrophils < 1.5 x 10 <sup>9</sup> /L	STOP Clozapine treatment immediately, or consult Clozapine Haematologist if wanting to continue therapy. Daily blood tests until results return to 'green' range. Then continue post-monitoring bloods for four weeks as per Section 5.7. Consult Haematology if guidance on management required, or if WCC and / or Neutrophil counts decrease further following withdrawal of Clozapine. <sup>15p16</sup>

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If the patient develops signs of infection and / or neutropenia (eg; flu-like symptoms, fever, sore throat or mouth ulcers), the medical officer should obtain an immediate FBC in addition to performing a clinical assessment of the patient.

If WCC and Neutrophil count are both normal, Clozapine therapy should continue in conjunction with twice weekly (i.e. within four days of each other) FBCs and clinical review until symptoms resolve.<sup>15p15</sup>

**Blood Result Entry:**

Inpatient FBC results and “dispensing events” should be entered into the patient profile on the ClopineCentral Database by the ward pharmacist.

Outpatient blood results and “dispensing events” should be entered by the Clozapine coordinator, or by the registered community pharmacist.

Medical Officers should also be aware how to access the ClopineCentral database and enter blood results in case patients present outside of usual working hours.

Red blood test results must be transmitted immediately to ClopineCentral.<sup>15</sup>

**Eosinophilia:**

Unexplained eosinophilia may occur, especially in the initial weeks of treatment with Clozapine. Discontinuation of therapy is recommended if the eosinophil count rises above  $3.0 \times 10^9/L$ . Therapy should restart only after the eosinophil count has fallen below  $1.0 \times 10^9/L$ .<sup>15</sup>

The Clopine Haematologist may be contacted if advice on management is required.

**5.5.3 Cardiac Monitoring**

Cases of myocarditis, some of which have been fatal, and cardiomyopathy have been reported in patients on Clozapine. Myocarditis is most commonly observed early in treatment, with most cases occurring around the third week of treatment (days 14 – 21).<sup>1</sup>

The [NSW Ministry of Health Policy Directive PD2012 005 - Clozapine-induced Myocarditis – Monitoring Protocol](#).<sup>1</sup> should be followed.

- Baseline Troponin I or T, CRP, ECG should be completed.<sup>1</sup>
- Baseline Echocardiogram is recommended.<sup>1</sup>
- Troponin I or T and CRP should be repeated at weeks 1, 2, 3, 4, 6 and 18, at 6 months, and thereafter every six months unless clinically indicated.<sup>1</sup>
- Blood pressure, pulse rate, respiration rate and temperature should be taken as per Section 5.5.1.

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- ECG should be repeated at week four <sup>26</sup> (and earlier if taking concurrent medication with the potential to prolong the QT<sub>c</sub> interval), and then at six months and annually thereafter unless clinically indicated.<sup>1</sup>
- Echocardiogram should be repeated at six months, then thereafter if clinically indicated.<sup>1</sup>
- Patients should be asked to report feeling unwell and any symptoms of illness including fever, chest pain, shortness of breath, flu-like symptoms, unexplained fatigue, severe diarrhoea, vomiting or dysuria.
- During the first four weeks, the patient should be directly asked about symptoms of myocarditis at least every alternate day whilst the patient is an inpatient, and weekly if the patient has been transferred to an outpatient clinic. <sup>1 p3</sup>

The [NSW Ministry of Health Policy Directive PD2012 005 - Clozapine-induced Myocarditis – Monitoring Protocol](#)<sup>1</sup> should be followed if patient develops:

- Signs or symptoms of unidentified disease, OR
- Pulse Rate  $\geq$  120bpm or increased by  $>$  30bpm, OR
- CRP  $\geq$  50mg/L, OR
- Troponin I or T elevation  $>$  ULN.

**5.5.4 Clozapine Plasma Levels**

- Indications for Clozapine plasma levels include:
  - Failure to respond to treatment
  - Presence of adverse effects
  - Suspicion of non-compliance
  - Complicating physical disease (especially hepatic disease)
  - Advanced age
  - Interacting drugs <sup>21</sup> (See Appendix 2)
  - Change in smoking status - Refer to NSW Ministry of Health Tools: <sup>3,4</sup>
    - [Tool03 - Clozapine and smoking cessation](#)
    - [Tool08 - Clozapine and consumers who resume or might resume smoking](#)
- Plasma levels may be useful in optimising therapy if poor response occurs; however, reported levels are often variable.<sup>8</sup>
- Patients show great variation in both their symptomatic response and side effects,<sup>23</sup> and may respond with a plasma level lower than the usual range.
- Sampling time:
  - Levels should be taken at least three days after a dose change.<sup>16 p3</sup>
  - The blood sample should be taken immediately before the next dose is due (trough level), or 12 hours post-dose if Clozapine is taken once daily.<sup>27 p3</sup>
  - N.B. Differences of a few hours in the time of evening dosing and / or morning plasma sampling will lead to large differences in reported plasma levels.<sup>23</sup>



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- Clozapine levels are processed at different times during the week at each campus. Clinicians should make themselves familiar with local pathology processing timetables.

**5.5.5 Metabolic Monitoring**

Parameter	Frequency
Fasting Glucose / HbA1c	<ul style="list-style-type: none"> <li>▪ Baseline</li> <li>▪ <u>Non-diabetic patients:</u></li> <li>▪ Fasting Glucose -               <ul style="list-style-type: none"> <li>➢ At 1 month, 3 months, 6 months, 9 months and 12 months<sup>16p45,121;28,29</sup></li> <li>➢ Then a minimum of six monthly thereafter, unless clinically indicated<sup>29</sup></li> </ul> </li> <li>▪ HbA1c –               <ul style="list-style-type: none"> <li>➢ Every 12 months</li> </ul> </li> <li>▪ <u>Diabetic patients:</u></li> <li>▪ HbA1c –               <ul style="list-style-type: none"> <li>➢ Every three months</li> </ul> </li> </ul>
Fasting Lipids (Total Cholesterol, HDL, LDL, Triglycerides)	<ul style="list-style-type: none"> <li>▪ Baseline</li> <li>▪ Every three months for first 12 months<sup>29</sup></li> <li>▪ Then a minimum of six monthly thereafter<sup>29</sup></li> </ul>
Weight, waist circumference and BMI (Metabolic Monitoring Form completed)	<ul style="list-style-type: none"> <li>▪ Baseline</li> <li>▪ Inpatients: Weekly</li> <li>▪ Outpatients: Monthly for first six months, then three monthly<sup>32</sup></li> </ul>

**5.5.6 Additional Recommended Monitoring**

Parameter	Frequency
LFTs	Baseline, then every six months
EUC	Baseline, then every six months

**5.6 Interruptions in Therapy**

**5.6.1 Recommencing Clozapine after therapy interruption**

Once Clozapine has been discontinued, the plasma level drops quickly, and tolerability to the adverse effects rapidly declines. Profound hypotension, collapse, and seizures are particular risks when re-starting Clozapine.

Therefore, if the interval since the last dose of Clozapine exceeds 48 hours, re-titration is necessary.

The patient should be advised to contact their doctor or case manager if they have missed taking Clozapine for more than two days, before taking their next dose.

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All patients recommencing Clozapine after an interruption of treatment must have a pre-treatment blood test. This includes patients with therapy interruptions of less than a week.<sup>15 p18</sup>

Manufacturers recommend that treatment should be restarted with a dose of 12.5mg – 25mg.

If the initial dose is tolerated, the dose may be re-titrated to the therapeutic level at a faster rate than recommended for initial treatment, provided the patient did not experience severe adverse effects from initial dose titration.<sup>15 p18</sup>

If the time since the last Clozapine dose is between 48-72 hours, it may be possible to start a rapid re-titration straight away. Dosing should be dependent on the patient's ability to tolerate prior doses.

A suggested dosing schedule is to restart with half of the previously prescribed total daily dose on day one (in divided doses 12 hours apart), 75% of the previous daily dose on day two, and if tolerated, the whole of the previous daily dose in the normal dosing schedule on day three.<sup>16p159</sup>

Physical observations should be performed as per new patients (see Section 5.5.1).

A “therapy event” must be entered into the ClopineCentral database by the ward Pharmacist or Clozapine Coordinator.

**5.6.2 Haematological Monitoring following Therapy Interruption**<sup>15 p18</sup>

Three days or less interruption of therapy:

- Continue monitoring as normal

More than three days and less than four weeks interruption of therapy:

- Weekly patients: Weekly FBC for the next six weeks, or until the original week 18 date, whichever is the later date. Then every four weeks thereafter.
- Monthly (four weekly) patients: weekly FBC for six weeks, then every four weeks thereafter.

Four weeks or more interruption of therapy:

- Recommence monitoring as for a new patient (weekly FBC for 18 weeks).

Any change to the monitoring frequency will show up on the ClopineCentral patient profile as an “active override”, or revised “week 18 date”, once the “therapy event” has been entered.

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If a patient has discontinued Clozapine therapy for three months or more, the patient must be re-registered with ClopineCentral by submitting a new Patient Registration Form, or via the ClopineCentral website (<https://www.clopine.com.au/ClopineCentral/>).

Clozapine must not be recommenced in patients who have previously developed blood dyscrasias related to Clozapine therapy,<sup>15 p18</sup> unless discussed with the Clopine Haematologist.

**5.7 Therapy Discontinuation**

A gradual reduction in dose is recommended over at least a one to two week period.<sup>14</sup> A reduction of 25mg/day each month is recommended.<sup>8</sup>

If abrupt discontinuation is required due to a serious adverse event, the patient's mental state should be monitored carefully.

The patient should also be observed for symptoms of cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.<sup>14</sup>

'Weekly' patients require a FBC to be performed at the time of discontinuation, then weekly for four weeks.

'Monthly' (four weekly) patients require an additional FBC close to the time of discontinuation, then four weeks after discontinuation.

Patients who are being monitored daily or twice weekly, due to red or amber blood counts or signs of infection, require testing to continue at this frequency until the blood count returns to the 'green' range or symptoms resolve. Monitoring frequency should then reflect their previous protocol, i.e. if they were weekly, they should receive four weeks of weekly blood tests.<sup>15 p18-18</sup>

Inform Clozapine coordinator or ward pharmacist in order to "cease" patient on ClopineCentral patient profile and ensure appropriate post-monitoring occurs.

Inpatient post-monitoring blood results should be entered into the ClopineCentral Database by the ward pharmacist.

Outpatient blood results should be entered by the Clozapine coordinator.

Medical Officers should also be aware how to access the ClopineCentral database and enter blood results.

**5.8 Reporting of Serious or Unexpected Adverse Effects**

ClopineCentral and the Clozapine coordinator / ward pharmacist should be notified of all serious or unexpected adverse events.

The treating medical officer should complete the Clopine Adverse Event Report Form and return to ClopineCentral, and also forward a completed [ADRAC Adverse Drug Reaction Reporting Form \("Blue Card"\)](#) to the TGA.

## **5.9 Transfer of Care**

### **5.9.1 Admission to SESLHD Inpatient Ward**

- Patient's usual dose should be determined, and compliance assessed.
  - If there is doubt about a patient's compliance (more than 48 hours since last dose), the duty or on-call consultant psychiatrist must be contacted for advice, before prescribing the dose (See Section 5.6.1).
  - A Clozapine level may be taken if appropriate. N.B. Clozapine levels are only processed once a week at some facilities. Staff should make themselves familiar with local pathology processing timetables.
- Patient must be registered with ClopineCentral at the hospital the patient is being admitted to.
- The Clozapine coordinator or ward pharmacist must be contacted at the earliest opportunity (Monday to Friday 8:30am – 5:00pm) to alert them to the patient, to organise patient transfer on the ClopineCentral database if necessary, and to ensure that the patient is up to date with relevant FBC monitoring.
- A FBC should be ordered if it is unknown when the last FBC was obtained.
- Assess smoking status. Refer to [NSW Ministry of Health Tool 03 – Clozapine and Smoking Cessation](#).<sup>3</sup>
- The on-call pharmacist should be contacted for advice and medication supply if the patient is admitted out of hours (to ensure doses are not missed).

### **5.9.2 Transfer to SESLHD from another centre:**

- The Clozapine coordinator or ward pharmacist should be contacted at the earliest opportunity to arrange transfer of the patient from the existing Clozapine Centre to SESLHD on the ClopineCentral database.

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- Patients who are taking a different brand of Clozapine must be registered with ClopineCentral using the ClopineCentral “Registration Form for patients switching from another Clozapine brand to Clopine”.<sup>15 p29</sup>

**5.9.3 Transfer to another centre from SESLHD**

- The Clozapine coordinator or ward pharmacist should be contacted to arrange ClopineCentral transfer of the patient from SESLHD to the new Centre on the ClopineCentral database.
- The treating medical officer, Clozapine coordinator, or ward pharmacist should contact the Clozapine coordinator at the receiving centre to discuss the transfer and confirm that the new Centre accepts responsibility for the monitoring of the patient.
- If the patient is being discharged, the treating medical officer should write a discharge prescription for enough Clozapine to last until the first Clozapine Clinic appointment (dependent on frequency of blood testing), and organise a pre-clinic blood test.

**5.9.4 Discharge from SESLHD-wards / units – Referral to Clozapine Clinic****New Patients:**

See Document 6.5 for a Referral Checklist.

It is the responsibility of the referring medical officer to ensure that the following have been done prior to referral:

- FBC, Troponin I or T, CRP, EUC, LFTs, fasting Cholesterol (including HDL, LDL, Triglycerides), fasting Glucose / HbA1c
- Metabolic Monitoring Form complete – Weight, Height, BMI, Waist Circumference, BP
- ECG
- Echocardiogram (recommended)

Abnormalities must be dealt with by the treating team before referral to the clinic.

**Existing Patients:**

All appropriate monitoring should be up to date. See Document 6.2 for a summary.

The medical officer should contact the Clozapine coordinator and / or Clozapine consultant to refer the patient to the Clozapine Clinic and arrange a clinic appointment. The case manager (where applicable) should also be contacted well in advance of discharge.

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The medical officer should inform the ward pharmacist of the discharge, and prescribe enough Clozapine to last until the clinic appointment (some overlap may be required if medications are blister packed – discuss with the ward pharmacist). N.B. Supply is dependent on an up to date FBC.

The medical officer should explain the process to the patient of attending a Pathology Collection Centre within the 48 hours prior to their scheduled Clozapine Clinic appointment, in order to have their weekly / four weekly blood test.

The patient should be informed of the Clozapine Clinic appointment date and time.

The patient should be provided with a Pathology Laboratory blood test request form, requesting a FBC and any other necessary blood tests.

The patient should be counselled on their discharge medication by the ward pharmacist (where available) or medical officer, and provided with the Consumer Medicines Information leaflet +/- the ClopineCentral “Your Guide to Clopine” information booklet. See Document 6.6 for recommended counselling points.

The medical officer should ensure the Discharge Summary is up to date on EMR before the patient attends the Clozapine Clinic.

The Nurse looking after the patient should ensure that the patient has the following before leaving the ward:

- Discharge medications (which have been explained to the patient by the pharmacist or medical officer)
- Pathology Laboratory blood test request form
- Clozapine Clinic appointment – and patient is aware of date and time

The Nurse should also ensure the case manager (if applicable) is aware of the discharge.

The following should be faxed or emailed to the Clozapine coordinator for inclusion in the Clozapine Clinic file:

- Baseline echocardiogram report (if available)
- Copy of baseline and any subsequent ECGs

For patients who may return to smoking on discharge, refer to NSW Ministry of Health [Tool 08 – Clozapine and consumers who resume or might resume smoking](#).<sup>4</sup>

**5.10 SESLHD Clozapine Clinics**

Patients must be referred to a Clozapine Clinic prior to discharge from all SESLHD wards / units.

The treating team must ensure that all monitoring detailed above is up to date prior to discharge of the patient (See Documents 6.1 and 6.2 for a summary).

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An adequate quantity of Clozapine tablets must be prescribed and dispensed to last the patient until their Clinic appointment (dependent on frequency of blood testing).

In the case of new patients who are referred to the Clozapine Clinic for Clozapine initiation as an outpatient, it is the responsibility of the referring medical officer to ensure that all baseline tests have been performed, and that the patient is registered with ClopineCentral prior to attendance at the clinic.

The SESLHD Clozapine Clinics are held each Wednesday at:

- POWH Euroa Centre
- St George Community Mental Health, Kogarah
- Sutherland Community Mental Health, Sutherland Hospital

Patients must attend a Pathology Laboratory within 48 hours of their scheduled appointment for a FBC (and any other necessary blood tests) to be taken.

During the first appointment, the prescribing medical officer should check that all relevant tests have been performed and documented by the referrer.

At each subsequent appointment, the medical officer should ensure that the necessary monitoring has been performed.

The Clozapine Monitoring Form should be completed on EMR.

Blood tests must be checked, and a prescription written each week during the first 18 weeks of treatment, then every four weeks thereafter, as per Section 5.10.2.

Patients should attend the Clozapine Clinic at least every three months (stable patients), or six months (highly supported, case managed patients). All patients on Clozapine maintenance are to have a face-to-face review by a Clozapine Clinic Consultant Psychiatrist or treating Consultant Psychiatrist at least every six months.

A letter should be sent to the GP at the first appointment and every 12 months.

Physical observations (blood pressure, pulse rate, temperature and respiration rate) should be taken weekly for the first four weeks of treatment. <sup>1 p3-4</sup>

Blood pressure should be repeated at weeks six and 18. <sup>1 p1</sup>

Blood pressure, pulse rate and temperature should then be measured three monthly thereafter, by the Clozapine Coordinator or outpatient nurse.

The medical officer should be informed if:

- Blood pressure:
  - Systolic <100 or >140mmHg
  - Diastolic <60 or > 90mmHg
  - OR a postural drop of 30mmHg
- Pulse rate: ≥100bpm or increased by > 30bpm
- Temperature: < 35.5°C or > 38°C
- Respiration rate : < 10 or > 25 breaths/min <sup>25 p15</sup>

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- Chest pain, shortness of breath

During the first four weeks of treatment, the patient should be directly asked about symptoms of myocarditis at each weekly Clozapine Clinic appointment. <sup>1 p3</sup>

The Clozapine coordinator should ensure that the physical metabolic monitoring (weight, BMI, waist circumference) is up to date. See Document 6.2 for a summary. Physical metabolic monitoring should be undertaken when due by the case manager (where available), local medical officer, or by the Clozapine coordinator.

**5.10.1 Keeping Body In Mind (KBIM) Referral Procedure**

Each clozapine site has a KBIM team that operates a healthy lifestyle clinic alongside the Clozapine Clinic.

Referrals should be made by the Clozapine coordinator into the electronic diary of a KBIM team member in available clinic time.

Appropriate referrals are for brief assessment and advice around diet, physical activity and smoking cessation.

Consumers should be referred into KBIM group programs for more intensive lifestyle modification.

**5.10.2 Outpatient Clozapine Prescribing**

After attendance at the clinic, patients should be provided with an outpatient prescription for Clozapine.

The prescription should be written for seven days' supply for patients who require weekly blood tests.

Prescriptions may be written for up to 28 days' supply for patients who have exceeded 18 weeks of therapy and are eligible for monthly (four weekly) blood tests.

Prescriptions for the first 18 weeks of treatment must be dispensed at the hospital pharmacy.

Prescriptions for continuing treatment (of patients who have completed at least 18 weeks of therapy and are on a stable dose) may also be dispensed by a Clozapine-registered Community Pharmacy (see Section 5.12).

Clozapine prescriptions to be dispensed at the hospital pharmacy must be written by a Clozapine-registered prescriber on a POWH/STGH/TSH Section 100 (S100) Prescription. All of the following information must be handwritten by the prescribing medical officer:

- Patient name, MRN, date of birth, address
- Drug name, form and strength(s) required to make up the dose
- Quantity of tablets of each strength (not number of days' supply)
- Streamlined Authority Code
  - NB. There are separate PBS streamlined authority codes for initial treatment and continuing treatment. (See [PBS Website](#) for up to date codes).



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- Prescriber name, PBS Prescriber Number, signature, date  
Clozapine (Clozapine) tablets are available in 25mg, 50mg, 100mg and 200mg strengths.  
No repeats may be issued on these prescriptions.

If Clozapine is being initiated in the community, the first prescription must be written by a consultant psychiatrist, to fulfil S100 criteria.  
See Document 6.7 for an example S100 prescription.

The medical officer should attach a Pathology Laboratory Blood Result Form to the prescription (POWH / TSH). The FBC should have been taken within 48 hours of the prescription date.<sup>15 p15</sup> The form should include the date, dose, and signature of the prescriber, and a note of any abnormal blood result or dose change.

At STGH, the FBC results are entered directly into the online ClozapineCentral patient profile by the Clozapine coordinator during the Clinic appointment, and these results must be checked by the pharmacist before dispensing Clozapine.

If the patient wishes the NSW Government to cover the cost of their co-payment, the prescriber must also provide a signed NSW Health Co-payment Consent Form with the prescription. The patient or representative must sign the form on collection of the medication. Each form is valid for one year, and should be kept on file by the pharmacy.

**5.10.3 Outpatient Clozapine Dispensing**

The WCC and Neutrophil results must be checked by a Clozapine-registered pharmacist before a prescription may be dispensed. Abnormal blood results should be discussed with the prescriber, if not already noted on the blood form.

Any discrepancies between the prescribed dose and previously dispensed doses should be investigated.

The prescription should then be dispensed as per POWH/STGH/TSH pharmacy procedures.

**5.11 Supply of Additional Medication to Patients**

If a patient will require an increased quantity of Clozapine, for example if travelling overseas, the prescribing medical officer or Clozapine coordinator must obtain a dispensation from ClozapineCentral, and document this clearly on the prescription that is sent to the pharmacy.

Patients must have an up to date FBC on their ClozapineCentral patient profile for dispensations to be approved.

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Request for up to 180 days medication supply may be approved, provided the patient is compliant with their mandatory blood tests whilst they are away.

If the patient has a green blood result history, the following may be approved:

- Monthly patients may have their blood test date extended by 14 days
- Weekly patients may have their blood test date extended by two days

**5.12 Community Pharmacy Clozapine Dispensing****5.12.1 Process for Transferring Patient to Community Pharmacy Dispensing**

N.B. Clozapine may only be dispensed for POWH/STGH/TSH patients by a community pharmacy registered as a “Clinic” with ClopineCentral, and associated with the relevant Hospital.

The patient must use same community pharmacy each time.

Suitability of patient for community pharmacy dispensing should be assessed:

- Patient must be on maintenance stage of therapy (i.e. must have completed 18 weeks of weekly FBCs)
- Patient should be stable on treatment, and be organised and compliant with medication, and / or have a case manager
- Patient must be informed of the changeover and be in agreement.

The SESLHD MH pharmacist should be contacted with the patient name and preferred community pharmacy or suburb.

The SESLHD MH pharmacist should then contact the community pharmacy to request community pharmacy dispensing, and organise Clopine registration and training where necessary.

The community pharmacy must be registered as a “Clinic” with Clopine Central, and associated with the relevant hospital.

All community pharmacists to be involved in dispensing Clozapine must be registered with ClopineCentral at that community pharmacy (Clinic), and follow the ClopineCentral Protocol for Clozapine dispensing.

The SESLHD MH pharmacist should provide the community pharmacy with the Clozapine Dispensing Transfer Form (includes last dose details and due date). See Document 6.8 for format.

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The SESLHD MH pharmacist or Clozapine coordinator must add the community pharmacy (Clinic) to the patient's ClopineCentral profile (to allow the community pharmacy access).

**5.12.2 Prescribing**

- Clozapine prescriptions to be dispensed at a community pharmacy must be prescribed on a PBS Authority Prescription, with the streamlined code annotated (See [PBS Website](#) for up to date codes). See Document 6.9 for example prescription.
- Clozapine cannot be brand-substituted. "Clopine" brand must be specified, and the "brand substitution not permitted" box must be crossed.
- One prescription is required per strength of tablet.
- If repeat prescriptions are required, a phone authority must be obtained, and the code annotated on the prescription. Up to five repeats may be authorised with a phone authority.
- Blood result forms must accompany each prescription (POWH, TSH). At STGH, blood results are entered electronically into the ClopineCentral patient profile by the Clozapine coordinator during the appointment. The community pharmacist must check these results before dispensing Clozapine for the patient.
- Any dose change must be indicated on the prescription or on the blood result form.
- A signed NSW Health Co-payment Consent Form must be provided annually to the Pharmacy, if the patient wishes NSW Health to cover the cost of the co-payment.

**5.12.3 Process for Amber / Red Results**

- Medical Officer must acknowledge amber result on blood form, and document when next blood test will be taken. The Clozapine coordinator and pharmacist must ensure the patient is aware of the amber result, when the next blood test is due, and the need to report any symptoms of infection.
- If a red result is obtained, the patient and community pharmacy must be contacted immediately to advise to cease clozapine and to organise repeat blood tests (as per Section 5.5.2). If the prescriber wishes to continue Clozapine, the Clopine Haematologist must be contacted. The outcome of this discussion must be communicated directly to the pharmacist, and documented in EMR and on the blood result form (with the date of the next blood test).
- Clopine Haematologist recommendations are visible in the "notes" section of the patient profile on the ClopineCentral database.

**Supply quantity:**

- Community pharmacy decision - preferred method should be confirmed with the pharmacy:

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- a) Clozapine Clinic to provide a new prescription with blood result form each week, *OR*
- b) Pharmacy to provide a “staged supply” of weekly medication whilst increased FBC monitoring is required (supply provided on receipt of signed blood test result form each week from doctor).

**5.12.4 Dispensing**

- Clozapine-registered community pharmacist must check blood results before dispensing Clozapine.
- Clozapine-registered community pharmacist must then promptly enter the blood results and “dispensing event” into the ClozapineCentral patient profile (unless already entered by the Clozapine coordinator).

Repeat Prescription Dispensing

- Repeat Prescription Dispensing is at the discretion of the community pharmacy
- Repeat prescriptions should be kept by the community pharmacy with the co-payment consent form (not returned to the patient).
- The Clozapine Clinic must fax through a blood test result form when due for dispensing.
- The blood test result form must be annotated by the medical officer with:
  - Confirmation of current Clozapine dose
    - If dose has changed, the doctor must supply new prescription.
  - Doctor’s name and signature
  - Date
  - Acknowledgement of any “amber” or “red” result, as above.

**5.12.5 Non-compliance / Re-titration**

- If a patient has been non-compliant for more than two days, the community pharmacy must contact the doctor or Clozapine coordinator immediately. Out of hours, the Acute Care Team may be contacted for advice, or the patient should be referred to the Emergency Department for review by a doctor.
- The “therapy event” must be entered into the Clozapine Central database by the Clozapine coordinator.
- A pre-treatment blood test should be taken before recommencing Clozapine.
- Changes to the **frequency of blood test monitoring** will apply if the patient has missed more than three days of Clozapine:
  - ≤ 3 days interruption
    - Continue four weekly monitoring as normal
  - ≥ 4 days and < 4 weeks interruption

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- Weekly FBC for six weeks, then back to four weekly
  - ≥ 4 weeks interruption
    - Weekly FBC for 18 weeks, then four weekly (as for new patient)<sup>15</sup>
- PBS requirements for: “Continuing Treatment” are that the dose must be stable and the patient must have completed 18 weeks of weekly FBC monitoring.
- Therefore initial re-titration doses must be dispensed by the hospital pharmacy (using the PBS “Treatment Phase: Initial Treatment” streamlined code - See [PBS Website](#) for up to date codes).
- Once the dose is stable, a decision should be made whether re-titration should be dispensed by the hospital pharmacy or by the community pharmacy, based on individual patient factors.
- N.B. If the patient has been non-compliant for more than four weeks, they would no longer be classed as being in the “continuing” stage of treatment. Therefore they would not be eligible for community pharmacy dispensing until they had completed the 18 weeks of weekly FBC tests.
- **Supply quantity:** seven days whilst in the “weekly” monitoring stage - Clinic to provide a new prescription with blood result each week.

**5.13 Outpatient Initiation of Clozapine****POWH / TSH:**

Contact Clozapine consultant for advice.

**STGH:**

The referring medical officer must contact the Clozapine coordinator and / or the consultant overseeing the Clozapine Clinic in advance to arrange outpatient initiation. All baseline tests should be completed prior to initiation (as per Section 5.3.2).

An agreement should be reached before initiation as to who is responsible for the necessary physical observation monitoring.

The patient must be registered with ClopineCentral before commencement of Clozapine. The Clopine Patient Number (CPN) must be documented in the patients EMR notes, and in the patients file.

A prescription for the first week’s supply of Clozapine should be sent to STG hospital pharmacy prior to the planned initiation date. This should be accompanied by a copy of the baseline FBC result (taken within 10 days of planned commencement date), and a signed NSW Health Section 100 Co-payment Consent Form.

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The patient should be placed in the Mental Health Unit (MHU) for the day to receive the first dose. A community clinician must attend the unit with them to perform the required observations.

Appropriate resuscitative facilities must be available.

The first dose of 12.5mg should be given in the morning.

Physical observations (BP (lying and standing), pulse rate, respiration rate and temperature) should be taken as follows:

- Baseline, then every half hour for two hours, then hourly for the following four hours after the first dose (six hours post-dose monitoring in total).

The medical officer should be informed if:

- Blood pressure:
  - Systolic <100 or >140mmHg
  - Diastolic <60 or > 90mmHg
  - OR a postural drop of > 30mmHg
- Pulse rate: > 100bpm or increased by > 30bpm
- Temperature: < 35.5°C or > 38°C
- Respiration rate : < 10 or > 25 breaths/min <sup>25 p15</sup>
- Chest pain, shortness of breath
- Patient is clearly over-sedated
- Patient is constipated
- Any other adverse effect is present. <sup>19 p161-163, 29 p15</sup>

Monitoring should continue thereafter as per local procedure.

As a minimum, monitoring should take place as per Document 6.4.

During the first four weeks, the patient should be observed closely for signs and symptoms of myocarditis, and directly asked about symptoms at least weekly (preferably every second day).<sup>2 p3</sup>

These include persistent tachycardia (although commonly benign), palpitations, shortness of breath, chest pain, fever, and arrhythmia.

Symptoms may also include cough, diarrhoea, nausea, vomiting, sore throat, myalgia, headache, sweatiness and urinary discomfort or frequency.<sup>2 p4</sup>

The patient must be advised to inform staff if they feel unwell, and to seek out-of-hours review if necessary.

ECG monitoring is recommended when Clozapine is prescribed in combination with other drugs known to prolong the QT<sub>c</sub> interval. ECG should then be repeated at week four,<sup>26</sup> at six months, and then annually thereafter.<sup>1 p1</sup>

The patient should be provided with a Pathology Laboratory blood test request form, requesting a FBC, Troponin I or T, CRP and any other necessary monitoring, and advised to have the blood test within the 48 hours before their Clozapine Clinic appointment.

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The patient should attend the Clozapine Clinic weekly for the first 18 weeks, and then every four weeks thereafter (or as determined by the medical officer).

**6. DOCUMENTATION**

**6.1 Clozapine Registration Check List**

Ensure the following have been completed:

<b>Eligibility</b>	Non-responsive to $\geq 2$ other antipsychotic drugs, or intolerant of other antipsychotic drugs due to side effects
	Contraindications are absent, cautions have been considered
	Medication Review - Drug Interactions have been considered - Plan made for withdrawal of existing antipsychotics
<b>Education</b>	Patient aware of benefits and risks associated with Clozapine treatment
<b>Consent</b>	Clozapine (Clozapine) Consent Form Signed by patient and Medical Officer (Document if patient unable to give informed consent)
<b>Investigations</b>	Blood Group (required for registration with ClozapineCentral)
	FBC - WCC & Neutrophil Count (within 10 days of intended commencement date - required for registration with ClozapineCentral)
	Baseline EUC, LFTs
	Baseline fasting Glucose (or HbA1c), fasting Lipids (including HDL, LDL, Triglycerides) (Metabolic Monitoring)
	Baseline Troponin I or T, CRP (Cardiac Monitoring)
	Baseline BP (lying and standing), Pulse Rate, Temperature, Respiration Rate (Physical Observations)
	Baseline ECG
	Baseline Echocardiogram (Recommended)
	Full Physical Exam
	Assess smoking status (affects Clozapine levels)
<b>Documentation</b>	Metabolic Monitoring Form completed (Weight, Height, BMI, Waist circumference, BP)
<b>Registration</b>	ClozapineCentral Patient Registration Form completed
	Inform Clozapine Coordinator or ward pharmacist

**Patient must not be commenced on Clozapine until confirmation of registration with ClozapineCentral has been received (confirmation received via email or via Clozapine Coordinator or ward Pharmacist).**

Document Clozapine Patient Number (CPN) in patient notes.

ClozapineCentral require 24 hours' notice in order to register a patient (discuss with Clozapine Coordinator or ward pharmacist if wishing to commence Clozapine more urgently).

**First dose of Clozapine should be given in the morning where possible (6 hours of post-monitoring required).**

Contact Clozapine Coordinator or ward Pharmacist with any queries.

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### 6.2 Clozapine - Monitoring Summary

	Monitoring Requirements
Pre-dose	Monitor BP, Pulse Rate, Temperature, Respiration Rate, etc. as per Clozapine Observation Monitoring Chart
Half hourly for 2 hrs, then hourly for 4 hrs post-first dose	Monitor BP, Pulse Rate, Temperature, Respiration Rate, etc. as per Clozapine Observation Monitoring Chart
BD for ≥ 4wks*	Monitor BP, Pulse Rate, Temperature, Respiration Rate, etc. as per Clozapine Observation Monitoring Chart * whilst an inpatient (refer to Document 6.4 for outpatient monitoring)
Weekly whilst an inpatient	Complete Metabolic Monitoring Form on EMR
Week 1	FBC, CRP, Troponin I or T (ECG if indicated)
Week 2	FBC, CRP, Troponin I or T (ECG if indicated)
Week 3	FBC, CRP, Troponin I or T (ECG if indicated)
Week 4	FBC, CRP, Troponin I or T, Fasting Glucose ECG
Week 5	FBC
Week 6	FBC, CRP, Troponin I or T, BP
Weeks 7 - 11	Weekly FBC
Week 12	FBC, Fasting Glucose / HbA1c, Fasting Lipids (Total Cholesterol, HDL, LDL, Triglycerides)
Weeks 13-17	Weekly FBC
Week 18	FBC, CRP, Troponin I or T, BP
Week 18 onwards	Every 4 weeks - FBC - ongoing whilst on Clozapine, and for 4 weeks after ceasing (refer to Section 5.7)

#### Ongoing Physical Observation Monitoring:

BP, pulse rate, temperature, respiration rate	Inpatients – as above. Outpatients – Week 1, 2, 3, 4 - BP, pulse rate, temperature, respiration rate. Week 6, 18 – BP Then three monthly thereafter – BP, pulse rate, temperature
---	---

#### Ongoing Cardiac Monitoring:

At 6 months	CRP, Troponin I or T - then 6 monthly thereafter unless clinically indicated ECG - then annually thereafter unless clinically indicated Echocardiogram - then thereafter if clinically indicated
-------------	--

#### Ongoing Metabolic Monitoring:

<ul style="list-style-type: none"> <li>▪ Fasting Glucose / HbA1c</li> </ul>	<ul style="list-style-type: none"> <li>▪ <u>Non-diabetic patients:</u></li> <li>▪ Fasting Glucose -               <ul style="list-style-type: none"> <li>➢ At 1 month, 3 months, 6 months, 9 months and 12 months</li> <li>➢ Then a minimum of six monthly thereafter, unless clinically indicated</li> </ul> </li> <li>▪ HbA1c –               <ul style="list-style-type: none"> <li>➢ Every 12 months</li> </ul> </li> <li>▪ <u>Diabetic patients:</u></li> <li>▪ HbA1c –               <ul style="list-style-type: none"> <li>➢ Every three months</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>▪ Fasting Lipids (Total Cholesterol, HDL, LDL, Triglycerides)</li> </ul>	Every three months for 12 months, and then a minimum of six monthly thereafter
<ul style="list-style-type: none"> <li>▪ Weight, waist circumference, BMI</li> </ul>	Inpatients: Weekly Outpatients: Monthly for first six months, then three monthly
<ul style="list-style-type: none"> <li>▪ BP</li> </ul>	As above for inpatients, then at every outpatient clinic appointment

#### Ongoing Monitoring:

Every six months	LFTs, EUC
------------------	-----------

#### Repeat more frequently if clinically indicated.

Refer to POWH Clinical Business Rule: Clozapine - Guidelines for Prescribing, Administration and Monitoring (Section 5.5.2) for WCC and Neutrophil ranges and monitoring requirements.

Refer to [NSW Ministry of Health Policy Directive PD2012\\_005 - Clozapine-induced Myocarditis – Monitoring Protocol](#).<sup>1</sup>



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### 6.3.1 Clozapine Observation Monitoring Chart (Inpatients) – Initiation (Day 1)

Attach Addressograph:

Complete observations as below, then twice daily thereafter

Date:		Baseline	+0.5h	+1h	+1.5h	+2h	+3h	+4h	+5h	+6h
Time:										
Blood Pressure: Lying										
Blood Pressure: Standing										
Pulse Rate										
Respiration Rate										
Temperature										
Chest Pain ( <i>Alert MO</i> )	Y/N									
Shortness of Breath ( <i>Alert MO</i> )	Y/N									
Sedation:	Y/N									
Absent	0									
Mild	1									
Severe	2									
Dizziness	Y/N									
Constipation	Y/N									
Hypersalivation:	Y/N									
Absent	0									
Mild	1									
Severe	2									
Headache	Y/N									
Perspiration	Y/N									
Nausea	Y/N									
Enuresis	Y/N									
Infection ( <i>if yes – alert MO - repeat FBC immediately</i> )	Y/N									
Signature										

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### 6.3.2 Clozapine Observation Monitoring Chart (Inpatients) – Day 2 Onwards

Attach Addressograph

Complete observations TWICE DAILY (pre-dose, and 4-6 hours post-dose (or pre-and post-dose if once daily evening dose)

Date:									
		AM	PM	AM	PM	AM	PM	AM	PM
Time:									
Blood Pressure: Lying									
Blood Pressure: Standing									
Pulse Rate									
Respiration Rate									
Temperature									
Chest Pain ( <i>Alert MO</i> )	Y/N								
Shortness of Breath ( <i>Alert MO</i> )	Y/N								
Sedation:	Y/N								
Absent	0								
Mild	1								
Severe	2								
Dizziness	Y/N								
Constipation	Y/N								
Hypersalivation:	Y/N								
Absent	0								
Mild	1								
Severe	2								
Headache	Y/N								
Perspiration	Y/N								
Nausea	Y/N								
Enuresis	Y/N								
Infection ( <i>if yes – alert MO - repeat FBC immediately</i> )	Y/N								
Signature									

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### 6.4 Clozapine Outpatients - Ongoing Monitoring - Summary

#### Months 1 – 6:

PARAMETER	Base -line	WEEK																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	22	26
<b>Haem</b>																					
FBC	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
<b>Physical *</b>																					
BP	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Pulse Rate	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Temp	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Resp Rate	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
<b>Cardiac</b>																					
Troponin I or T	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
CRP	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
ECG	*	□	□	□	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Echo	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
<b>Metabolic</b>																					
Gluc / HbA1c	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Lipids	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Waist/ Weight/ BMI	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
<b>Other</b>																					
EUC	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
LFTs	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

□ ECG if indicated (e.g. interacting medications)

#### Month 7 Onwards:

PARAMETER	MONTH						THEN THEREAFTER				COMMENTS
	7	8	9	10	11	12	Every month (4 weekly)	Every 3 months	Every 6 months	Every 12 months	
<b>Haem</b>											
FBC	*	*	*	*	*	*	*				4 Weekly thereafter unless amber / red result or therapy interruption. Refer to Sections 5.5.2 and 5.6
<b>Physical</b>											
BP		*	*	*	*	*	*				Refer to Section 5.13 for physical observations if Clozapine is being initiated in the community
Pulse Rate		*	*	*	*	*	*				
Temp		*	*	*	*	*	*				
<b>Cardiac</b>											
Troponin I / T					*	*	*		*		6 monthly thereafter unless clinically indicated
CRP					*	*	*		*		6 monthly thereafter unless clinically indicated
ECG									*		Annually thereafter unless clinically indicated
Echo											Thereafter if clinically indicated
<b>Metabolic</b>											
Gluc / HbA1c		*	*	*	*	*	*		*		At least 6 monthly thereafter
Lipids		*	*	*	*	*	*		*		At least 6 monthly thereafter
Waist/ Weight/ BMI		*	*	*	*	*	*	*			3 monthly thereafter
<b>Other</b>											
EUC					*	*	*	*	*		6 monthly thereafter
LFTs					*	*	*	*	*		6 monthly thereafter

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### 6.5 Referral to Clozapine Clinic - Process on Discharge

**\*\* Please contact Clozapine coordinator and ward pharmacist well in advance of discharge \*\***

Responsibility	Process
Referring Doctor	<ul style="list-style-type: none"> <li>▪ Ensure the following have been done prior to referral:               <ul style="list-style-type: none"> <li>▪ Blood Group (if new patient)</li> <li>▪ FBC, EUC, LFTs, Fasting Cholesterol (Total Cholesterol, HDL, LDL, Triglycerides), Fasting Glucose / HbA1c, Troponin I or T,* CRP*</li> <li>▪ Echocardiogram (recommended)*, ECG*</li> <li>▪ Metabolic Monitoring Form complete – Weight, Height, BMI, Waist Circumference, BP</li> </ul> </li> <li>▪ Abnormalities must be dealt with by the treating team before referral to the Clinic</li> </ul> <p style="text-align: right;">*If due</p>
Referring Doctor	<ul style="list-style-type: none"> <li>▪ Assess smoking status.</li> <li>▪ Refer to NSW Health Tool 08 – <a href="#">Clozapine and consumers who resume or might resume smoking</a>.<sup>4</sup></li> </ul>
Referring Doctor	<ul style="list-style-type: none"> <li>▪ Contact Clozapine Coordinator and / or Clozapine Consultant to refer patient and arrange Clinic appointment</li> </ul>
Referring Doctor	<ul style="list-style-type: none"> <li>▪ Inform Case Manager of discharge plan (if applicable)</li> </ul>
Referring Doctor	<ul style="list-style-type: none"> <li>▪ Inform Pharmacist of discharge &amp; Rx enough Clozapine until Clinic appointment (some overlap may be required if blister packed – d/w ward pharmacist) N.B. Supply is dependent on up to date FBC</li> </ul>
Referring Doctor	<ul style="list-style-type: none"> <li>▪ Explain process to patient re. weekly / 4 weekly blood tests within 48 hours before Clozapine Clinic appointment.</li> <li>▪ Inform patient of Clozapine Clinic appointment date &amp; time</li> </ul>
Referring Doctor	Provide patient with Pathology Blood Request Form for: <ul style="list-style-type: none"> <li>▪ FBC</li> <li>▪ Any other tests e.g. Troponin I or T, CRP (if due)</li> </ul>
Pharmacist	<ul style="list-style-type: none"> <li>▪ Organise discharge medication</li> <li>▪ Liaise with Community Pharmacy for community pharmacy dispensing or blister packing if applicable</li> </ul>
Pharmacist (where available)	<ul style="list-style-type: none"> <li>▪ Counsel patient on discharge medication (See Document 6.6)</li> <li>▪ Provide Consumer Medicines Information (CMI) leaflet +/- ClopineCentral “Your Guide to Clopine” booklet (If no ward pharmacist available, Doctor to do same)</li> </ul>
Referring Doctor	<ul style="list-style-type: none"> <li>▪ Ensure Discharge Summary complete on EMR</li> </ul>
Nurse	Ensure patient has the following <u>before</u> leaving the ward: <ul style="list-style-type: none"> <li>▪ Discharge Medications (<b>and explained by Pharmacist / Medical Officer</b>)</li> <li>▪ Pathology Blood Request Form</li> <li>▪ Clozapine Clinic Appointment – patient aware of date and time</li> </ul> Ensure Case Manager aware of discharge (if applicable)
Referring Doctor	Ensure the following are faxed / emailed to Clozapine Coordinator: <ul style="list-style-type: none"> <li>▪ Baseline Echocardiogram Report (if available)</li> <li>▪ Copy of baseline and any subsequent ECGs</li> </ul>

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**6.6 Clozapine Patient Counselling**

<p>Written information provided:</p> <ul style="list-style-type: none"> <li>▪ CMI</li> <li>▪ ClopineCentral "Your Guide to Clopine" Information Booklet</li> <li>▪ Healthy eating leaflets</li> </ul>
<p>Blood test (FBC) monitoring:</p> <ul style="list-style-type: none"> <li>▪ Reason for monitoring</li> <li>▪ Report symptoms of infection</li> <li>▪ Weekly FBC for 18 weeks (specify week 18 date), then every four weeks thereafter</li> <li>▪ Blood test on Monday/ Tuesday, Clozapine Clinic on Wednesday                             <ul style="list-style-type: none"> <li>➤ Check patient has blood form and appointment date and time</li> </ul> </li> </ul>
<p>Compliance</p> <ul style="list-style-type: none"> <li>▪ Importance of compliance</li> <li>▪ What to do if missed &gt; 2 days of Clozapine</li> </ul>
<p>Enquire about current side effects</p>
<p>Drowsiness Dizziness</p> <ul style="list-style-type: none"> <li>▪ Increased effects of alcohol</li> <li>▪ Avoid driving if drowsy or dizzy</li> </ul> <p>Constipation</p> <ul style="list-style-type: none"> <li>▪ Recommend high fibre diet, plenty of fluids, regular exercise</li> <li>▪ Inform Doctor / Case Manager promptly if this occurs</li> </ul>
<p>Metabolic:</p> <ul style="list-style-type: none"> <li>▪ Healthy diet, regular exercise (provide healthy eating leaflets)</li> <li>▪ Cholesterol, blood sugar monitoring</li> <li>▪ Report symptoms of diabetes</li> </ul>
<p>Smoking</p> <ul style="list-style-type: none"> <li>▪ Encourage smoking cessation</li> <li>▪ Explain effects on clozapine levels of reducing or quitting smoking</li> <li>▪ Inform Doctor if planning to cut down</li> </ul>
<p>Cardiac monitoring:</p> <ul style="list-style-type: none"> <li>▪ Reason for monitoring</li> <li>▪ Monitoring requirements</li> <li>▪ Report symptoms of myocarditis</li> </ul>

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**6.7 Example Clozapine Section 100 (S100) Prescription**

**PRESCRIPTION** \*ONLY valid for supply to hospital patients at this Hospital Pharmacy **XXXXX**

- Royal Hospital for Women**  
Barker St, Randwick Ph: 9382 6111  
(Provider Number 0010070L)
- Prince of Wales Hospital and Community Health Service**  
Barker St, Randwick Ph: 9382 2222  
(Provider Number 0010260H)
- Sydney Children's Hospital**  
High St, Randwick Ph: 9382 1111  
(Provider Number 0012870J)

MRN 1234567 If patient label used, clinician to print patient name and check label correct

FAMILY NAME Smith GIVEN NAME(S) John

ADDRESS 2 High Street

DATE OF BIRTH 09 / 09 / 1979 MALE / FEMALE WEIGHT \_\_\_\_\_ WARD/CLINIC PSYOP

ALLERGY/ADR NKA Pregnant / Breast Feeding / NA

Patient's Medicare number					Pharmaceutical benefits entitlement or DVA number																	
1	2	3	4	5	6	7	8	9	0	1												
<input type="checkbox"/> Safety Net entitlement card holder					<input type="checkbox"/> Concessional or dependant, RPBS beneficiary or Safety Net concession card holder																	

DETAILS MUST BE COMPLETE BEFORE MEDICINES CAN BE SUPPLIED

Narcotic prescriptions: Above Patient Details in Prescribers Handwriting, ONE item per page, Quantity in Words AND Numbers  
PLEASE DELETE UNUSED LINES

DRUG NAME & FORM (Generic in Block Letters)	STRENGTH	DOSE/ROUTE/ DIRECTIONS	QUANTITY	REPEATS Outpatients Only	S100 STREAMLINED AUTHORITY NUMBER (if required)
<i>CLOZAPINE tab</i>	<i>100mg</i>	<i>ONE tab po nocte</i>	<i>28</i>	<i>0</i>	<i>4998</i>
<i>CLOZAPINE tab</i>	<i>200mg</i>	<i>TWO tabs po nocte</i>	<i>56</i>	<i>0</i>	<i>4998</i>

FOR DISCHARGE PRESCRIPTIONS ONLY: MEDICATION LIST REQUIRED? YES / NO Page \_\_\_ of \_\_\_

Name of Prescriber (PRINT) w DOCTOR Prescriber Number 1234567

Designation Psychiatry Page / Contact Number 44444

Signature of Prescriber *W Doctor* Date 6 / 9 / 2017

I certify that I have received this medication and the information relating to any entitlement to free or concessional pharmaceutical benefits is not false or misleading.

\_\_\_\_\_  
Date of supply      Patient or agent's signature      Agent's address

S0642 - 091014

○ BINDING MARGIN – DO NOT WRITE ○

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6.8

**SESLHD PHARMACY**

**CLOZAPINE – COMMUNITY PHARMACY DISPENSING TRANSFER FORM**

<b>Patient Name</b>	<b>D.O.B.</b>
<b>MRN</b>	<b>Clopine Number</b>
<b>Address</b>	
<b>Case Manager</b>	

<b>Community Pharmacy</b>
---------------------------

Community Pharmacy added as "Clinic" on Clopine Central Patient Profile: (Tick: )

Date of Last Supply:
Dose Dispensed:
Quantity Supplied (Number of Days):

Tablet strengths supplied:

Strength of Tablet	Dose	Quantity

Next blood test due:
<b>Next Supply Due:</b>

Name of Pharmacist	Signature	Date
--------------------	-----------	------

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### 6.9 Example Clozapine PBS Authority Prescription – Community Pharmacy Dispensing

**PBS - RPBS authority prescription**  
Not valid unless authorised by delegate

X *Dr Clopine*

The Maroubra Centre  
130 Garden Street  
MAROUBRA NSW 2035

Patient's Medicare no. 1234-56789-11 Patient's Ref no. 11

Patient's full name ANTHONY PATIENT

Patient's address 1, MAROUBRA RD, MAROUBRA Postcode 2035

Tick for return to patient

Entitlement no. \_\_\_\_\_

Safety Net entitlement  Concessional or dependant, RPBS beneficiary or Safety Net concession cardholder

**Authorisation is requested for the following:**  
(Tick appropriate boxes)

PBS prescription from state manager, Medicare Australia

RPBS prescription from the authorised delegate of the Repatriation Commission

Brand substitution not permitted

Only one item per form

Clopine 100mg tabs

Dosage directions T nocte

Quantity 28 Prescriber's signature \_\_\_\_\_ Date \_\_\_\_\_

No. of repeats 0 Phone/Delegate approval 312 16 4998

Quantity \_\_\_\_\_ Repeats \_\_\_\_\_ Phone/Delegate approval \_\_\_\_\_

I declare that I have received this medicine and the information relating to any entitlement to a pharmaceutical benefit is correct.

Patient's or agent's signature \_\_\_\_\_ Date of supply 1/1

Agent's address \_\_\_\_\_

Privacy notice: The information on this form, including your Medicare, Centrelink and/or Department of Veterans' Affairs number, will be used to assess your entitlement to benefits under the Pharmaceutical Benefits Scheme (PBS) or the Repatriation Pharmaceutical Benefits Scheme (RPBS) and to determine payments due to approved suppliers. This information will also be used to record details of an under-compound prescription (where there is no entitlement to a payment of benefit under PBS or RPBS). With your consent, the PBS approved supplier or PBS Prescriber may store your details for use on future prescriptions. The collection of this information is authorised by the National Health Act 1953. This information may be disclosed to PBS Prescribers, the Department of Health and Ageing, Department of Veterans' Affairs, Centrelink, the Department of Human Services or its authorised or required by law. 4006\_05/11

Disease or purpose for which benefit required or clinical justification for use of item

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
Patient's age if under 18 \_\_\_\_\_

Has the patient previously received an authority for this medicine? Yes  No

Prescriber's phone no. \_\_\_\_\_

Phone approvals - retain this copy for 12 months.  
Written approvals - forward all 3 copies to Medicare Australia/DVA.

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### 7. AUDIT

Regular monitoring of IIMS relating to Clozapine.  
Physical Health Audit Program.



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### 8. REFERENCES

#### 8.1 RELATED POLICIES/PROCEDURES/GUIDELINES/BUSINESS RULES

Number	Policy/Procedure/Guideline/Business Rule	Grade of Recommendation
1.	<a href="#">NSW Ministry of Health PD2012_005. Clozapine-induced Myocarditis - Monitoring Protocol.</a> 19 Jan 2012	A
2.	<a href="#">SESLHD Policy SESLHDPD/182 "Off-label use of registered medicines and use of unlicensed medicines.</a> July 2015	
3.	NSW Ministry of Health Publication/Tool-03 – <a href="#">Clozapine and Smoking Cessation</a>	A
4.	NSW Ministry of Health Publication/Tool-08– <a href="#">Clozapine and consumers who resume or might resume smoking</a>	A
5.	NSW Health Policy PD2013_043 <a href="#">Medication Handling in NSW Public Health Facilities.</a> Updated 27 Nov 2013	A
6.	Australian Commission on Safety and Quality in Health Care – <a href="#">National Inpatient Medication Chart for Adult Patients (NIMC)</a>	A

#### 8.2 INTERNAL REFERENCES

Number	Reference	Grade of Recommendation
7.	SESLHD Procedure SESLHDPR/283 - <a href="#">Patient with Acute Condition for Escalation (PACE): Management of the Deteriorating Adult and Maternity Inpatient.</a> August 2016	A
8.	The Sutherland Hospital Mental Health Service - Clozapine Prescribing Guidelines, Dr William Andrews. Last updated: Dec 2013	
9.	SESLHD Adult Clozapine Titration Chart (adapted from Australian Commission on Safety and Quality in Health Care: National Adult Clozapine Titration Chart)	A
10.	MHRU Clozapine Observation Monitoring Record Sheet – Day 1	B
11.	MHRU Clozapine Observation Monitoring Record Sheet – Day 2 Onwards	B
12.	SEALS Pathology Clozapine Plasma Level Reference Range	A
13.	POWH In-house Clozapine Clinic Protocol (Not Published), Dr Shuli Futeran.	A

#### 8.3 EXTERNAL REFERENCES

Number	Reference	Grade of Recommendation
14.	MIMS Online - Clopine Product Information. Last revised 1 Nov 2014.	A
15.	ClopineCentral Clozapine Manual – Your Clozapine Support. Jan 2015	A
16.	D. Taylor <i>et al.</i> The Maudsley Prescribing Guidelines in Psychiatry, 12 <sup>th</sup> Edition. Wiley-Blackwell, 2015. ISBN 978-1-118-75460-3	A
17.	Australian Prescriber. Medicines Safety Update No. 1; 2011. Clozapine and severe constipation.	A
18.	NSW Health Safety Notice 017/11 – Clozapine and Smoking Cessation – Potential Toxicity. 6 December 2011	A
19.	MIMS Online – Clopine Consumer Medicine Information Leaflet. April 2015.	A

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20.	Clopine (Clozapine) Monitoring System Privacy Statement. Hospira. Dec 2014.	N/A
21.	Hospira product information - "Clopine® (Clozapine) Drug Interactions"	A
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**9. REVISION AND APPROVAL HISTORY**

Date	Revision No.	Author and Approval
November 2015	Version 1	Lisa John Pharmacist - Clozapine Working Group, POWH
December 2015	Version 2	Peter Baldas – District Policy Support Officer
January 2016	Version 3	Lisa John Pharmacist - Clozapine Working Group, POWH
February 2016	Version 4	Discussion at the Document Development Committee February 2016 to establish consultation process
July 2016	Version 5	Endorsed by District MHS Clinical Council.
September 2017	Draft	Formatting reviewed by Executive Services
September 2017	Draft	Endorsed by DQUM Committee with minor change to document using terms "client" and "patient".
November 2017	0	Endorsed by SESLHD Clinical and Quality Council for publishing.

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May 2018	0	Risk rating changed from High to Medium – approved by Executive Sponsor
June 2019	1	Amended to reflect all patients on Clozapine maintenance are to be reviewed by a Consultant Psychiatrist at least every six months.
August 2019	1	“Review” defined as a face-to-face consultation. Endorsed by SESLHD Mental Health Service DDCC. Endorsed by SELSHD Mental Health Service Clinical Council. Minor review approved by Executive Sponsor. Published by Executive Services.

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**APPENDIX 1: Management of Side Effects associated with Clozapine therapy** 9,16p165-6,177-178

Adverse Effect	Time Course	Action
Neutropenia / Agranulocytosis	More common in first 18 weeks, but may occur at any time.	See Section 5.5.2 - Blood Count Monitoring. Admit to hospital if agranulocytosis occurs. Symptoms may include fever, flu-like symptoms, sore throat or mouth ulcers.
Myocarditis / Cardiomyopathy	Myocarditis – usually early in treatment Cardiomyopathy – may occur at any time.	Follow the <a href="#">NSW Ministry of Health Policy Directive PD2012_005: Clozapine-induced Myocarditis – Monitoring Protocol</a> . <sup>1</sup> See Section 5.5.3 – Cardiac Monitoring.
Constipation	First 4 months are the highest risk. Usually persists.  Common adverse effect with a prevalence of up to 60%. When constipation is severe, the fatality rate is around 20-30%.	Counsel patients about the risk of constipation and question about bowel movements. Ensure adequate fibre (≥ 20-25g/day), fluids (1.5-2L/day) and exercise (≥150mins/week). Initiate treatment promptly if constipation is suspected or reported. Bulk-forming laxatives may be used. Use an osmotic and / or stimulant and stool-softening laxative (e.g. docusate & senna) early if any signs of constipation. Assess for bowel obstruction. Review other medications that may be contributing and reduce Clozapine dose if possible. <b>Effective prevention and treatment of constipation is essential to prevent serious, potentially fatal complications</b> including intestinal obstruction, ischaemia and perforation.  Immediate medical attention required if abdominal pain, distension, vomiting, overflow diarrhoea, absent bowel sounds, acute abdomen, feculent vomitus or symptoms of sepsis occur. Case reports of fatalities occurring only hours after first symptoms present, therefore prompt assessment and management required.
Hypotension (postural) - may cause dizziness	First 4 weeks.	Advise patient to take time when standing up. Reduce dose / slow rate of titration.
Hypertension	First 4 weeks, sometimes longer.	Monitor closely, increase dose slowly. Antihypertensive therapy is sometimes necessary. Longer term, weight gain may lead to hypertension.
Tachycardia	First 4 weeks, but sometimes persists.	Very common in early stages of treatment but usually benign. Tachycardia, if persistent at rest and associated with fever, hypotension or chest pain, may indicate <b>myocarditis</b> . Follow the <a href="#">NSW Ministry of Health Policy Directive PD2012_005: Clozapine-induced Myocarditis – Monitoring Protocol</a> . <sup>1</sup> See Section 5.5.3 – Cardiac Monitoring Benign sinus tachycardia may be treated with a beta-blocker. Prolonged tachycardia may precipitate cardiomyopathy.
Fever	First 3 weeks	Fever is not usually related to blood dyscrasias, but be alert for <b>myocarditis</b> or <b>NMS</b> . Give antipyretic, but check FBC, CK, CRP and Troponin. Reduce rate of dose titration.
Sedation	First few months. May persist but usually wears off to some extent.	Give smaller dose in the morning. Reduce dose / slow rate of titration if necessary. Check Clozapine level.
Weight gain	Usually during the first year of treatment.	Weight gain is common and often profound. <b>Dietary counselling is essential</b> - recommend healthy diet and regular exercise. Advice may be more effective if given before weight gain occurs. Minimise antipsychotic polypharmacy (with exception of considering aripiprazole for reducing clozapine dose). <sup>35</sup>
Nausea	First 6 weeks	Anti-emetic may be prescribed. Consider GORD.
Hypersalivation	First few months. May persist, but sometimes wears off. Often very troublesome at night.	Manage according to severity of symptoms. See literature for pharmacological options. <sup>16 p174-5</sup> e.g. Atropine 1% eye drops administered sublingually or in a small amount of water as a mouthwash, or hyoscine hydrobromide 300microg tablets sucked / chewed up to tds.
Nocturnal enuresis	May occur at any time. May resolve spontaneously but may persist for months or years.	May affect 1 in 5 people on Clozapine. Try manipulating dosing schedule to avoid periods of deep sedation. Avoid fluids, and empty bladder before bedtime. Consider pharmacotherapy. <sup>16p166</sup>
Seizures	May occur at any time.	More likely with rapid titration / high dose / high Clozapine level. Consider prophylactic antiepileptic drug if high dose / Clozapine level. EEG abnormalities are common in those on Clozapine.

# SESLHD PROCEDURE

## Clozapine - Guidelines for Prescribing, Administration and Monitoring

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### APPENDIX 2: Clozapine Drug Interactions<sup>21</sup>

Common Clozapine interactions are summarised below. Please note: This list is not exhaustive. Further information on drug interactions may be obtained from the Clozapine Product Information<sup>14</sup>, available from MIMS Online via CIAP, or by contacting the hospital's Pharmacy Department.

Drug	Potential Pharmacodynamic Interaction
Drugs with potential to depress bone marrow function	Potential additive depression of bone marrow function
Alcohol, monoamine oxidase inhibitors (MAOIs) and CNS depressants such as narcotics, antihistamines and benzodiazepines	Clozapine may enhance central effects of these drugs
Benzodiazepines Other antipsychotics	May have increased risk of circulatory collapse, which on rare occasions may be profound; may lead to cardiac and / or respiratory arrest
Drugs with anticholinergic, hypotensive or respiratory depressant effects, or those known to prolong the QTc interval	Possibility of additive effects
Lithium CNS active agents	May increase the risk of development of neuroleptic malignant syndrome (NMS)
Valproate	Rare but serious reports of seizures and isolated cases of delirium Mechanism of this interaction has not been determined

Drug	Potential Pharmacokinetic Interaction
Highly protein bound drugs (eg; warfarin, digoxin)	Competition for protein binding sites may result in changes in plasma levels of Clozapine and other highly protein bound drugs
Inhibitors of cytochrome P450 enzyme system, in particular CYP1A2, CYP2D6, and CYP3A4 Eg; Azole antifungals Caffeine Cimetidine Ciprofloxacin Erythromycin, Clarithromycin, Azithromycin, Protease Inhibitors	May increase plasma levels of Clozapine
SSRIs	Elevated serum levels of Clozapine have been reported in patients receiving the drug in combination with fluoxetine, paroxetine, sertraline (up to twofold), fluvoxamine (up to tenfold) or citalopram Raised serum levels may also occur with escitalopram
Inducers of cytochrome P450 enzyme system Eg; Carbamazepine (CYP3A4) Phenytoin (CYP3A4) Rifampicin (CYP3A4) St John's Wort (CYP3A4) Omeprazole (CYP1A2)	May reduce plasma levels of Clozapine
Tobacco smoke	Known to induce CYP1A2 and may decrease plasma levels of Clozapine. Smoking cessation may lead to a rapid increase in Clozapine plasma levels (levels will start to rise within 24 hours and reach a new steady state after about 1 week). Consider a dose reduction of 30-50% if the patient stops smoking. Note that it is the components of tobacco smoke and not nicotine that induce CYP1A2. <b>Refer to NSW Ministry of Health Tools:</b> <a href="#">Tool-03: Clozapine and smoking cessation</a> <sup>3</sup> <a href="#">Tool-08: Clozapine and consumers who resume or might resume smoking</a> <sup>4</sup>