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# NIMC (clozapine titration) User Guide

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#### Acknowledgment

This work was developed by Queensland Health Safe and Quality Use of Medicines of Medication Services Queensland, Queensland Health Clozapine Working Party and representatives from Royal Brisbane and Women's Hospital, Logan Hospital, Mackay Hospital and Ipswich Hospital.

Additional editing to reflect the NIMC (clozapine titration) was provided by the Australian Commission on Safety and Quality in Health Care. This document is available on the Commission's website at <a href="https://www.safetyandquality.gov.au/our-work/medication-safety/medication-charts/national-standard-medication-charts/clozapine-titration-chart/">https://www.safetyandquality.gov.au/our-work/medication-charts/national-standard-medication-charts/clozapine-titration-chart/</a>

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## NIMC (clozapine titration) User Guide

The National Inpatient Medication Chart (NIMC) is a standardised tool for communicating patient medication information consistently between health professionals.

The NIMC (clozapine titration)<sup>1</sup> is an ancillary NIMC and is designed to be used in conjunction with either the NIMC (acute) or NIMC (long-stay). It was made available nationally in 2012.

The NIMC (clozapine titration) is a version of the Queensland Health clozapine titration chart (modified for national use), which resulted from the significant work of Queensland Health Safe and Quality Use of Medicines, Medication Services Queensland, the Clozapine Working Party and representatives from Royal Brisbane and Women's, Logan, Mackay and Ipswich hospitals.

The most recent updates made to the NIMC (clozapine titration) and this user guide have been informed by consultation with medication safety experts, and review of the Queensland health and Western Australia Health clozapine titration charts.

## 1. Purpose

- The NIMC (clozapine titration) is intended to be used as a record of the prescribing, monitoring and administration of clozapine titration for adult inpatients.
- The NIMC (clozapine titration) should be used for patients who are on a titrating clozapine regimen. Maintenance doses should be ordered on the NIMC.

## 2. General instructions

- The NIMC (clozapine titration) is a legal document and therefore must be written in a clear and unambiguous form. All orders are to be written in ink. No matter how accurate or complete an order is, it may be misinterpreted if it cannot be read. Water soluble ink (e.g. fountain pen) should not be used. Black ink is preferred.
- Every clinician administering clozapine has a responsibility to ensure they can clearly read
  and understand the order before administering any medicines. For all incomplete or unclear
  orders, the prescriber should be contacted for clarification. Never make any assumptions
  about the prescriber's intent.
- Every NIMC (clozapine titration) must have the patient's identification details completed.
- The NIMC (acute) or NIMC (long-stay) it is used in conjunctions with should be clearly
  marked to indicate the ancillary NIMC (clozapine titration) is in use. The NIMC should be
  completed, including all patient safety features such as VTE risk assessment, as per local
  protocol.

- Every clozapine order must be complete and include:
  - date
  - route ('Oral' pre-printed)
  - generic drug name ('Clozapine' pre-printed)
  - dose ordered in metric units and Arabic numerals ('mg' pre-printed)
  - frequency ('Morning' and 'Evening' pre-printed)
  - times ('0800' and '2000' are pre-printed)
  - prescriber's signature
- A medicine order is valid only if the authorised prescriber enters all the required items.
- Dangerous abbreviations must be avoided. Only accepted abbreviations may be used (refer to <u>Recommendations for terminology, abbreviations and symbols used in medicines</u> documentation).
- No erasers or "whiteout" can be used i.e. orders MUST be rewritten if any changes are made, especially changes to dose and/or frequency
- Doses must be written using metric and Arabic (1, 2, 3) systems. Never use Roman numerals (i, ii, iii, iv).
- Never use a trailing zero (.0) after a decimal point as it may be misread if the decimal point is missed (e.g. 1.0 misread as 10)

#### Consistent documentation allows accurate interpretation of orders

The NIMC (clozapine titration) is intended to reflect best practice and assist clinicians to safely prescribe, dispense, administer and reconcile clozapine orders, monitor patients commencing on a clozapine titration regimen and minimise the risk of adverse drug events.

National, state and territory legislation, regulation and policies apply to ensure this highly specialised, and high risk, medicine is prescribed, dispensed, administered and monitored safely. Current requirements include:

- registration with a clozapine patient monitoring service
- pre-commencement blood and metabolic screening
- ongoing blood and metabolic monitoring

#### Implementation, education and evaluation resources

The Commission makes available a range of materials to support use of the NIMCs including NIMC (clozapine titration).

The resources are available on the Commission's website at <a href="https://www.safetyandquality.gov.au/our-work/medication-safety/medication-charts/national-standard-medication-charts/">https://www.safetyandquality.gov.au/our-work/medication-safety/medication-charts/national-standard-medication-charts/</a>

## 3. NIMC (clozapine titration) pages 1 and 2

#### 3.1 Patient location

#### **Purpose**

To establish the patient's location and record the clozapine patient number

NIMC (clozapine titration)								
Facility/service:								
Ward/unit:Year: 20								
Clozapine patient number (CPN):								

Figure 1 above shows the NIMC (clozapine titration) patient location and clozapine patient number details section

#### Use

- Record the facility name and ward or unit name on pages 1 and 2
- Fill in the pre-printed year space 20\_\_\_\_\_
- Record the clozapine patient number (CPN) which is issued by the Clozapine Monitoring Centre for the specific brand of clozapine chosen for patient treatment.

For example Clozaril<sup>R</sup> Patient Monitoring System, ClopineCentral<sup>™</sup>

#### Risk addressed

Patient location details are additional patient identification information.

Requiring the CPN on the chart before ordering commences ensures that the appropriate registration process has occurred.

Figure 2 below shows the clozapine registration prompt

Do not prescribe clozapine until approved by Clozapine Monitoring Centre and Clozapine Patient Number allocated

## 3.2 Cross-referencing the NIMC (clozapine titration) on the current NIMC

#### **Purpose**

To cross-reference the NIMC (clozapine titration) to the patient's main medication chart, the NIMC (acute) or NIMC (long-stay)

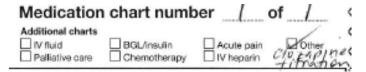


Figure 3 above shows the NIMC (acute) and NIMC (long-stay) additional charts section with use of the NIMC (clozapine titration) chart cross-referenced to it

#### Use

- Tick the 'Other' box in the NIMC additional charts section
- Write clozapine titration under or next to the ticked 'Other' box

#### Risk addressed

Alerting other health professionals that a NIMC (clozapine titration) chart is in use reduces the chance of missed or duplicate doses.

#### 3.3 Patient identification

#### **Purpose**

To establish the patient's identity before prescribing commences

#### Affix patient identification label here



Figure 4 above shows the NIMC (clozapine titration) identification section

#### Use

- Adhere a patient identification label in the space provided or hand write the patient UR number, first and family name, date of birth and gender in legible print on pages 1 and 2
- If a printed patient identification label is used, the first prescriber must check the patient's identity and print the patient's name under the labels to document confirmation that it is the correct patient

- Clozapine should not be administered if the prescriber does not document the patient identification
- An additional patient identification space is provided on the top of page 3 (see below)

#### Risk addressed

Not correctly identifying patients can result in missed or incorrect doses or patients being ordered or administered the wrong medicine.

#### Figure 5 below shows the additional patient identification space at the top of page 3

Family name:	Given name(s):	URN:

## 3.4 Allergies and ADR alert

#### **Purpose**

To communicate the existence of previous adverse drug reactions, allergies and related information

### Attach ADR sticker

(See current NIMC for details)

#### Figure 6 above shows the NIMC (clozapine titration) ADR sticker section

#### Use

- Reference previous ADRs, allergies and related details noted on the NIMC
- Fix an ADR alerts sticker on page 2 of the NIMC (clozapine titration) chart if patient has an ADR or allergy

#### Risk addressed

Failure to communicate previous ADRs and allergies can result in re-prescribing of offending medicines and avoidable patient harm.

## 4. NIMC (clozapine titration) pages 2 and 3

## 4.1 Prescribing titrating clozapine

#### **Purpose**

To document clozapine prescribing

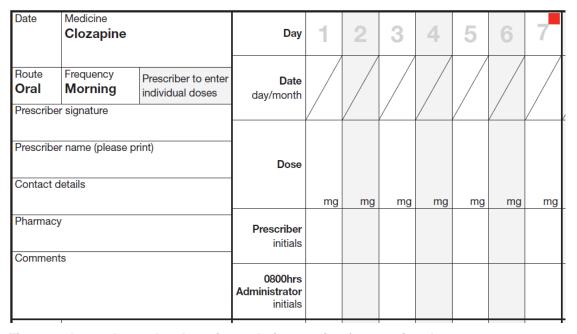


Figure 7 above shows the clozapine ordering section for morning doses

#### Use

- Record the date the medicine order is written
- Enter the date (day and month) for each day clozapine is prescribed along the horizontal date section
- Clozapine is pre-printed and there is space available for specifying a suspension or tablet if required
- If once daily doses only are prescribed, the prescriber must strike out the section ('morning'
  or 'evening') which will not be used (see Figure 8 below).
- Strike doses which are not required (see Figure 9 below).
- Prescriber signs the order and prints name and contact details (see Figure 9 below)
- Daily orders should be entered and each one initialled (see Figure 9 below)

#### Risk addressed

Standardising medicines prescribing and administering, and presentation of related information, reduces the risks of error through slips and lapses.

Figure 8 below shows morning order and administration sections struck out

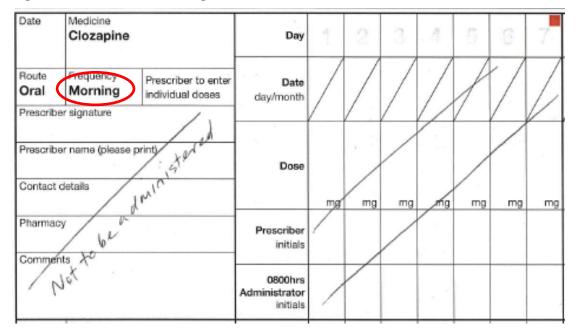
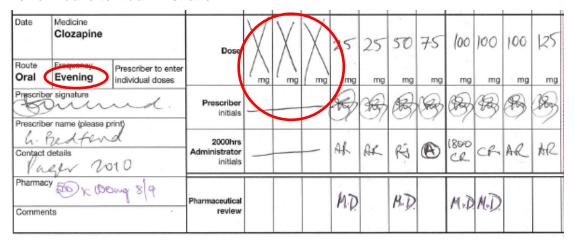


Figure 9 below shows the first three days of evening doses not required struck out to reduce the risk of inadvertent administration



### • Clozapine titration schedule

Figure 10 below shows the suggested clozapine titration schedule. This table is a guide only. A rapid or slower titration schedule may be required.

Clozapi	Clozapine titration schedule (this table is a guide only)													
If rapid or slower titration required refer to the treating psychiatrist.  In an attempt to minimise side effects the following dosing schedule is suggested:														
Day	1 2 3 4 5 6 7 8 9 10 11 12 13 14											14		
Morning	12.5mg	25mg	50mg	50mg	50mg	50mg	50mg	50mg						
Evening 25mg 25mg 50mg 75mg 100mg 100mg 125mg 125mg 125mg 150mg														
Titration be	Titration beyond 200mg/day: If well tolerated, the daily dose may be increased slowly in increments of 25–50mg.													

#### Restarting clozapine titration

Figure 11 below shows the guidance provided on restarting clozapine titration after a break of greater than forty-eight hours

## Dosing recommendations if clozapine dose is missed for greater than 48 hours

- Obtain psychiatric review prior to recommencing clozapine.
- Recommence at 12.5mg once or twice daily on the first day. If well tolerated, the dose may be increased slowly as suggested in the Clozapine titration schedule (on page 2 opposite).

This is a guide only – for further dosing options refer to treating psychiatrist.

For frequency of blood testing required, refer to Blood monitoring section (on page 4).

## 4.2 Ceasing titrating clozapine

#### **Purpose**

To document ceased medicines

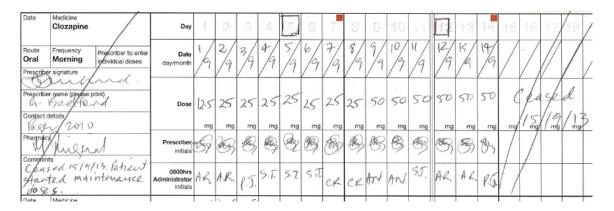


Figure 12 above shows ceased clozapine order

#### Use

- Strike out the order but leaving it legible
- Write the reason for changing the order, the date and initial
- A new order should be written if an order needs to be increased or decreased

#### Risk addressed

Clearly ceasing orders reduces the risk of inadvertent administration. Clearly communicating reasons for the change enables medication reconciliation at discharge.

## 4.3 Recording administration of titrating clozapine

#### **Purpose**

To document clozapine administration

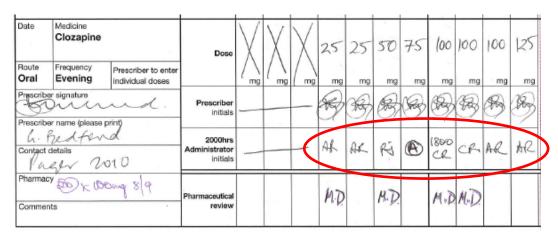


Figure 13 above shows the clozapine evening administration section

#### Use

- Check patient identity, check dose direction, administer medicine
- Initial order
- Write the time clozapine was administered above the initials if not administered at 0800 or 2000 (the pre-printed administration times)
- Enter appropriate code if dose not administered and circle it. Notify prescriber if the dose is refused by the patient.
- If the dose is withheld, document reason in the patient's medical notes.

#### Risk addressed

Standardising medicines prescribing and administering, and presentation of related information, reduces the risks of error through slips and lapses.

Circling the reason for not administering code prevents confusion with initials.

Figure 14 below shows the reason for not administering code legend

Reason for not administering  Codes MUST be circled										
Absent	A	On leave	(L)							
Fasting	F	Not available – obtain supply or contact prescriber	N							
Refused – notify prescriber	R	Withheld – enter reason in clinical record	W							
Vomiting	V	Self administered	S							

It is appropriate to withhold the medicine if:

- there is a known allergy or adverse drug reaction to clozapine
- the NIMC (clozapine titration) is full (i.e. there is no space to sign for administration) then the
  medicine order is not valid. A new NIMC (clozapine titration) must be written as soon as
  possible.

Generally medicines should not be withheld if the patient is pre-operative or nil by mouth / fasting unless specified by the prescriber.

#### 4.4 Pharmaceutical review

#### Purpose

To document pharmaceutical review of medicines orders



Figure 15 above shows the pharmaceutical review document space

#### Use

- Review all orders to ensure they are clear, safe and appropriate for the patient
- Initial in space provided
- Additional notes to clarify the order may be recorded by the pharmacist in the 'Pharmacy' box (see Figure 13 above)

#### Risk addressed

Unclear, unsafe and inappropriate medicine orders can risk patient safety.

## 4.5 Monitoring clozapine titration

#### **Purpose**

To provide advice and prompts for patient monitoring during clozapine titration

## Clozapine blood results monitoring system

Clozapine can cause a reduction in the number of white blood cells in patients and regular blood sampling is required to identify this. An alert system which gives guidance on whether therapy should be continued or ceased according to the patient's blood result is provided on page 3.

Figure 16 below shows the clozapine blood results monitoring table and decision support

Clozapine bl	ood results monitoring system	Recommended action
Green Range	WBC greater than 3.5 x 10°/L and	Continue clozapine therapy.
	Neutrophils greater than 2.0 x 10 <sup>9</sup> /L	
Amber Range	WBC 3.0-3.5 x 10 <sup>9</sup> /L	Continue clozapine therapy with twice-weekly
	or	blood tests until return to 'green' range.
	Neutrophils 1.5–2.0 x 10 <sup>9</sup> /L	
Red Range	WBC less than 3.0 x 10 <sup>9</sup> /L	Stop clozapine therapy immediately. Refer to local
	or	clozapine protocol for management guidelines.
	Neutrophils less than 1.5 x 10 <sup>9</sup> /L	

### Weekly monitoring

Figure 17 below shows the weekly monitoring prompt

Conduct weekly blood monitoring as indicated in Clozapine monitoring on page 1

A red-coloured square is printed on days 7, 14, 21 and 28 as a reminder that patients require

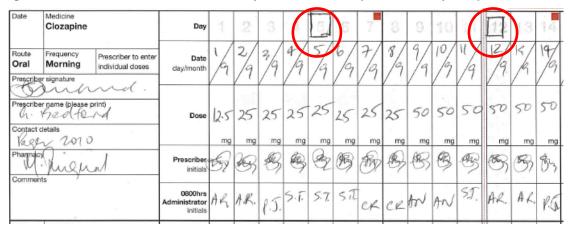
A red-coloured square is printed on days 7, 14, 21 and 28 as a reminder that patients require blood or metabolic monitoring on a weekly basis as indicated in the baseline measurements section of the clozapine monitoring table on page 1.

Figure 18 below shows the pre-printed weekly blood monitoring square



Additional tests may be indicated by the prescriber drawing a darkened line around the day box on the required day for testing (see Figure 19 below).

Figure 19 below shows additional weekly test reminders penciled in by the prescriber



## 5. NIMC (clozapine titration) page 4

#### 5.1 Pre-commencement

In order to minimise the effect of haematological adverse events, health professionals treating patients with clozapine are required to register their patients with the relevant Clozapine Monitoring Centre.

All patients, prescribers, dispensing pharmacists, clozapine coordinators and centres using clozapine must be registered with the Clozapine Monitoring Centre.

Refer to local protocol or guidelines for pre-commencement tests and specific paperwork requirements needed to commence a patient on clozapine, including requirement to complete a high-cost eligibility form.

#### Figure 20 below shows suggested pre-commencement actions

Pre-commencement	
Assess current smoking status	Complete clozapine patient registration form and send to
<ul> <li>Review and document medical history, cardio-metabolic risk factors</li> </ul>	Clozapine Monitoring Centre. To be approved before prescribing
and drug interactions	Inform your local clozapine coordinator
Assess bowel habits, including presence of any unnecessary	Provide pharmacist with blood test results and prescription
anticholinergic or other constipating agents	Complete high cost eligibility form
<ul> <li>Provide and explain clozapine brochure to consumer and family/carer</li> </ul>	Complete clozapine baseline monitoring (see page 1)

## 5.2 Blood monitoring

All patients recommencing clozapine following an interruption in treatment must have a pretreatment blood test. This includes patients with therapy interruptions of less than a week.

#### Figure 21 below shows suggested actions for restarting clozapine titration

#### **Blood monitoring**

If clozapine dose missed for 72 hours or less:

- Monitoring should continue as normal with no additional requirements
- If clozapine dose missed for 72 hours but less than 4 weeks:
- During the first 18 weeks monitor weekly for at least 6 weeks or for as long as necessary to achieve a total of 18 weeks monitoring.
   For example, if therapy is interrupted:
  - $-\,$  a) after 15 weeks, monitor with weekly blood tests for 6 weeks after clozapine is recommenced
  - $-\,$  b) after 9 weeks, monitor with weekly blood tests for 9 weeks after clozapine is recommenced
- Consumers on monthly monitoring monitor weekly for 6 weeks then continue with monthly monitoring if no problems detected If clozapine dose missed for 4 weeks:
- Monitoring should recommence as for a new consumer

## 5.3 Reviewing the patient including observation protocol

The patient should have a regular medical and nursing review as per local protocol to identify adverse reactions and effectiveness of clozapine treatment. The observation protocol on the NIMC (clozapine titration) at page 4 provides suggested monitoring guidelines. Advice can be sought from the treating psychiatrist if a different titration regimen is required.

#### Figure 22 below shows the suggested observation protocol

#### Observation protocol Refer to local protocol. Where unavailable, Medical Officer to select applicable observation protocol below. First ever clozapine dose Re-titration after treatment break (over 48 hours since last dose) 1. Prior to clozapine dose take baseline temperature, pulse, respiration (TPR) 1. Prior to clozapine dose take baseline temperature. and lying and standing blood pressure (BP) pulse, respiration (TPR) and lying and standing blood 2. Administer clozapine as prescribed pressure (BP) 2. Administer clozapine as prescribed 3. Repeat observations: Repeat observations: • 30 minutes after dose then TWICE daily (default, unless alternate option · every half an hour for 2 hours completed below by Medical Officer) · every hour for 4 hours minutes after dose then ...... daily 4. If above observations are outside normal parameters, 4. If above observations are outside normal parameters, seek medical review seek medical review Subsequent dose: 1. Observations should be recorded at least twice daily - TPR and lying and standing BP half an hour after a dose is administered. In inpatient settings more frequent observations are appropriate (as per local protocol). Observations should continue for 28 days where possible, unless a Medical Officer provides alternative directions on the required frequency and duration of physical observations Smoking: If change in smoking status notify Medical Officer

Patients must be kept under close supervision and their vital signs monitored for six hours following the first dose of clozapine. Any adverse events associated with the initial and subsequent doses need to be referred to a doctor and recorded. Subsequent doses should have vital signs monitored twice daily and continue for 28 days where possible.

#### **Temperature**

Transient elevations of temperature are most common in the first four weeks of treatment. Raised temperatures above 38°C should be investigated to rule out the possibility of underlying infection, neutropaenia or neuroleptic malignancy syndrome.

#### **Pulse**

Clozapine is associated with an increased risk of myocarditis, especially in the first 2 months of treatment. Cases of cardiomyopathy have also been reported. Persistent tachycardia at rest, or tachycardia accompanied by palpitations, arrhythmias, chest pain, shortness of breath or symptoms of heart failure should be urgently investigated for myocarditis or cardiomyopathy. If myocarditis or cardiomyopathy is diagnosed or suspected, stop clozapine and refer to a cardiologist.

#### **Blood Pressure (lying and standing)**

Hypotension and circulatory collapse may be profound and may be accompanied by cardiac and / or respiratory arrest. This occurs most commonly during the titration period. This risk is reduced by small, slow increases in dose. The patient should be closely supervised and lying and standing blood pressure monitored to record the presence of a postural drop.

#### **Smoking Status**

A change in smoking status can have an adverse effect on the patient's clozapine blood levels. Abrupt cessation of smoking may lead to clozapine intoxication. Patients that smoke should be informed that if they reduce or stop smoking, they are encouraged to do so, but must inform their nurse or doctor as a dose adjustment may be necessary.

## 5.4 Management of adverse effects

Clozapine treatment has well documented adverse effects, some of which are life threatening. All adverse effects, whether expected or unexpected, should be reported immediately to the Therapeutic Goods Administration (TGA) (and no later than three working days after the reaction) either <u>online</u> or using the '<u>blue card</u>' (Report of suspected adverse reaction to medicines and vaccines).

A list of some adverse effects, as well as the time course and recommended action, has been included on page 4 of the NIMC (clozapine titration) (see Figure 23 below). The recommended actions section includes both medical and nursing responses that can be used if an event occurs.

Figure 23 below shows the suggested management of side effects associated with clozapine therapy

Managemer	nt of common adverse effects	with clozapine therapy (suggested guidelines only)
Adverse effect	Time course for onset	Recommended actions
Neutropenia / Agranulocytosis	First 18 weeks (but may occur at any time)	Refer to Clozapine blood results monitoring system table on page 3. Admit to hospital if agranulocytosis is confirmed. Symptoms may include a sore throat or fever.
Myocarditis /	Myocarditis - within 6-8 weeks of starting	Cease clozapine. Admit to hospital if myocarditis or cardiomyopathy is confirmed.
Cardiomyopathy	Cardiomyopathy - may occur at any time	May present with flu-like symptoms.
Constipation	Usually persists and requires continuous monitoring/treatment – Clozapine Induced Gastrointestinal Hypomotility (CIGH)	Severe CIGH can be fatal and should be treated aggressively. Advise patients of risks before commencing and importance of monitoring. Recommend high-fibre diet, fluids, exercise and laxatives (such as docusate with senna or macrogol).
Sedation	First few months May persist, but usually wears off	Give smaller dose in the morning. Reduce dose if necessary – check plasma level.
Hypersalivation	First few months	Manage according to severity of symptoms. See literature for
Hypersalivation	Very troublesome at night	pharmacological options.
Hypotension	First 4 weeks	Reduce dose or slow down rate of increase. Advise consumer to slowly stand up from a lying or sitting position.
Hypertension	First 4 weeks, but sometimes longer	Increase dose slowly. Hypotensive therapy may be necessary.
Tachycardia	First 4 weeks, but sometimes persists	Common in early stages. If persistent at rest and associated with fever, hypotension or chest pain may indicate myocarditis. Refer to cardiologist.
Weight gain	Usually during the first year of treatment	Ensure dietary counselling before weight gain occurs.
Fever	First 4 weeks	Give antipyretic, perform urgent FBC and cardiac enzymes. Seek urgent medical review.
Seizures	May occur at any time	If seizures develop, check clozapine levels, seek neurology consult, order EEG and consider starting anti-seizure medication. Withhold clozapine for one day, and restart at half the previous dose.
Nausea	First 6 weeks	May give anti-emetic. Avoid prochlorperazine and metoclopramide if caused previous Extra Pyramidal Side Effects. Consider Gastro Oesophageal Reflux Disease (GORD).
Nocturnal enuresis	May occur at any time	Review dose schedule. Avoid fluids before bedtime. Seek medical review.
This is not an exhaust	ive list of side effects. Please see product information	for further advice.

<sup>•</sup> Modified from: Taylor D, Barnes T, Young A. The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition Wiley Blackwell 2021.

## 6. Clozapine monitoring

Clozapine is associated with a number of serious adverse effects such as blood dyscrasias, myocarditis and cardiomyopathy and regular monitoring can allow early detection of serious adverse effects. Patients require a full medical examination prior to the planned commencement of clozapine. Blood and metabolic monitoring of patients is required at baseline and regular intervals, as guided by local protocol. White blood cell count and neutrophil blood count are required to be registered with the Clozapine Monitoring Centre prior to dispensing clozapine.

A check list of investigations for clozapine monitoring is provided in the table on page 1 of the NIMC (clozapine titration) (see Figure 24 below). These are suggested guidelines only and the treating psychiatrist may request further tests according to the clinical results or hospital protocol policy.

Baseline tests required should be indicated by the prescriber by ticking the 'if required' column. This column may also be used to indicate if specific tests are required e.g. instead of ordering a full blood count (FBC), a neutrophils test may be ordered. There is a section for baseline, day 7, 14, 21 and 28 test results to be documented. The shaded sections indicate that these tests are not necessary at this time, unless required as per local protocol, or at the request of the treating psychiatrist. The last column of the chart indicates the recommended frequency of each test after the initial titration period.

If any of these results are outside normal parameters, or if results reveal particular physical health concerns, these should be raised with the treating team who must make a decision on whether or not to proceed with the prescribed course of treatment.

It is expected that the patient results will be checked and recorded primarily by medical officers using the check list on the NIMC (clozapine titration) with references for normal and abnormal test parameters available from the pathology system and documented in the clinical notes.

The suggested clozapine monitoring investigations in the NIMC (clozapine titration) have been modified from the Maudsley Prescribing Guidelines<sup>2</sup>.

Figure 24 below shows the suggested clozapine monitoring investigations

	required					F	lesults							
Investigations			E	Date (day 7): D				Date (day 14): Date (day 21):				day 28):	After 28 days	
		Baseline		•	11		1 1		/ /		/ /			
	(S)	Date completed	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal		
Full blood count (FBC)														
White blood cell (WBC)													Then continue weekly first 18 weeks then monthly	
Neutrophils														
Eosinophils														
Troponin – high sensitivity I or T													Then at 6 week then 3 months	
C-reactive protein (CRP)													Then as per loc protocol	
Electrocardiograph (ECG)													Then continue	
Liver function test (LFT)													as per local protocol	
Urea and electrolytes (U&E)													protocor	
Blood group														
Plasma glucose – fasting													Then at 3 month then every 6 months	
Total cholesterol – fasting														
Low density lipoprotein (LDL) – fasting														
High density lipoprotein (HDL) – fasting														
Triglycerides - fasting														
Beta human chorionic gonadotropin (Beta HCG) – female			-										As required	
Cardiac ECHO													Then continue	
Clozapine level (can help guide therapeutic dose)													as per local protocol	
Full physical exam													protocoi	
Height				ш										
Weight				kg		kg		kg		kg		kg		
Waist				cm								cm	Then continue monthly	
BMI [weight (kg)/height (m²)]														
Constipation			Check bowel habits daily for 4 weeks									Continue week		
Smoking – cigarettes per day													As required	

These are suggested guidelines only, refer to the treating psychiatrist for individual monitoring requirements. Check pathology system for test parameters.

Modified from: Taylor D, Barnes T, Young A. The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition Wiley Blackwell 2021.

#### **Full blood count (FBC)**

A pre-treatment full blood count is a requirement for registering a patient with the Clozapine Monitoring Centre. The test is to be repeated weekly for 18 weeks and then monthly. The results are recorded and sent to the Clozapine Monitoring Centre prior to prescribing. The NIMC (clozapine titration) has an area for recording this result for four weeks and the subsequent results are then recorded in the clinical file.

#### White blood count (WBC)

Clozapine can only be commenced if a white blood cell count (WBC) is greater than  $3.5 \times 10^9$ /L. If the WBC is 3.0– $3.5 \times 10^9$ /L, the blood test should be repeated in one week. If the blood results remain in this range clozapine treatment can commence under medical supervision. The results are sent to the Clozapine Monitoring Centre for recording prior to writing the order. This blood test is to be done weekly for 18 weeks and then monthly.

#### **Neutrophils**

A neutrophil count of greater than 2.0 x 10<sup>9</sup>/L is required to commence clozapine treatment. The results are sent to the Clozapine Monitoring Centre for recording prior to writing the prescription. This blood test is to be done weekly for 18 weeks and then monthly.

#### **Eosinophils**

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 and at the discretion of the treating psychiatrist. This blood test is to be done weekly for 18 weeks and then monthly.

#### **Troponin**

The presence of non-specific cardiac symptoms and family history of heart failure should be noted. Testing to measure the baseline markers of myocardial damage include using a troponin I or T assay and serum creatinine. Alternatively, where a troponin test is not available, creatine kinase monobasic isoenzyme (CK-MB) could be used. This blood test is to be done weekly for 6 weeks, then at 3 months, then as per local protocol.

#### C-reactive protein (CRP)

CRP is a non-specific marker of inflammation and may provide an early warning of the development of myocarditis caused by clozapine. This blood test is to be done weekly for 6 weeks, then at 3 months, then as per local protocol.

#### Electrocardiograph (ECG)

A baseline ECG is required and then as per local protocol.

#### Liver function test (LFT)

Baseline liver function tests are required. If results are outside normal parameters, commencement of clozapine is at the discretion of the treating psychiatrist. It is recommended that liver functions be tested annually.

#### **Urea and electrolytes (U&E)**

A baseline U&E test is required. It is recommended that U&E be tested annually.

#### **Blood** group

This is required for registration and identification purposes by the Clozapine Monitoring Centre.

#### Plasma glucose - fasting

This is required for registration with the Clozapine Monitoring Centre.

#### Total cholesterol - fasting

Increases in cholesterol levels have been observed in patients taking clozapine; a baseline level should be taken prior to commencing.

#### Low density lipoprotein (LDL) - fasting

A baseline LDL level is required. It is recommended to be tested at 3 months and then every 6 months.

#### High-density lipoprotein (HDL) - fasting

A baseline HDL level is required. It is recommended to be tested at 3 months and then every 6 months.

#### Triglycerides - fasting

A baseline triglyceride level is required. It is recommended to be tested at 3 months and then every 6 months.

#### Beta human chorionic gonadotropin (Beta HCG) - female

A beta HCG test should be done to confirm if the patient is pregnant. The adverse pharmacological and toxicological effects of clozapine in adults may also occur in the foetus. Therefore, clozapine should not be used in pregnancy or in women likely to become pregnant, unless the expected benefit of treatment is considered to outweigh the potential risk to the foetus.

#### **Cardiac ECHO**

It is advised that patients undergo echocardiography to test for the development of adverse cardiac events and to provide a baseline reading against which any future events may be measured. Then to be tested as per local protocol.

#### Clozapine level

When a patient has ceased clozapine and is being considered for re-titration or recommencement, a serum clozapine level needs to be measured prior to initiation. Clozapine level may help guide therapeutic dose and the frequency of this test is at the discretion of the treating psychiatrist.

#### Full physical exam

A full medical examination is required prior to commencement of clozapine

#### Height

Height is recorded in metres to assist with body mass index calculation.

#### Weight

An area has been provided for a base line and weekly recording of a patient's weight in kilograms (and in which "kg" is pre-printed).

#### Waist

A baseline waist measurement is required and recorded in centimetres with "cm" pre-printed on the NIMC (clozapine titration). Then continue measuring monthly, or as per local protocol, as an increase in waist measurement is a sign of weight gain.

#### **Body Mass Index (BMI)**

Body mass index is a simple calculation using a person's height and weight.

The formula is BMI = [weight (kg)/height (m<sup>2</sup>)]

where (kg) is a person's weight in kilograms and (m<sup>2</sup>) is their height in square metres.

#### Smoking - cigarettes per day

Baseline smoking habits, followed by weekly recordings, should be documented. Abrupt cessation of smoking may lead to clozapine toxicity. Patients who smoke need to inform their prescriber if they reduce or stop smoking as dose adjustment may be necessary.

#### Constipation

A gastrointestinal history and abdominal examination should occur before commencing clozapine. Bowel habits are to be recorded at baseline and then daily for 4 weeks. After 28 days monitoring should continue weekly.

Constipation or Clozapine Induced Gastrointestinal Hypomotility (CIGH) is a common adverse effect of clozapine treatment, which requires continuous monitoring/treatment. Severe CIGH can be fatal so prompt assessment and management is needed, which may include cessation of clozapine treatment. There should be a low threshold for patients to seek urgent medical attention when conservative management fails, or constipation is severe and acute

Signs and symptoms that warrant immediate medical attention include nausea and/or vomiting, abdominal distension and/or pain, spurious diarrhoea (overflow), absent bowel sounds, lack of urge and/or inability to defecate, acute abdomen, and symptoms of sepsis.

## References

- 1. Australian Commission on Safety and Quality in Health Care. NIMC (clozapine titration). Sydney: ACSQHC; 2023.
- 2. Taylor D, Barnes T, Young A. The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition Wiley Blackwell 2021.