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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 <https://www.safetyandquality.gov.au/our-work/medication-safety/medication-charts/national-standard-medication-charts/clozapine-titration-chart/>

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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)¹ 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 [Recommendations for terminology, abbreviations and symbols used in medicines 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

<https://www.safetyandquality.gov.au/our-work/medication-safety/medication-charts/national-standard-medication-charts/>

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[®] Patient Monitoring System, ClopineCentral[™]

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)

Medication chart number 1 of 1

Additional charts

<input type="checkbox"/> IV fluid	<input type="checkbox"/> BGL/insulin	<input type="checkbox"/> Acute pain	<input checked="" type="checkbox"/> Other
<input type="checkbox"/> Palliative care	<input type="checkbox"/> Chemotherapy	<input type="checkbox"/> IV heparin	clozapine titration

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

URN:

Family name:

Given names:

Address:

Date of birth:

Sex: ☐ M ☐ F

Not a valid prescription unless identifiers present

First prescriber to print patient name and check label correct:

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

Date	Medicine Clozapine		Day	1	2	3	4	5	6	7
Route Oral	Frequency Morning	Prescriber to enter individual doses	Date day/month							
Prescriber signature			Dose							
Prescriber name (please print)										
Contact details				mg	mg	mg	mg	mg	mg	mg
Pharmacy										
Comments			Prescriber initials							
			0800hrs Administrator initials							

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

Date	Medicine Clozapine		Day	1	2	3	4	5	6	7
Route	Frequency Morning	Prescriber to enter individual doses	Date day/month							
Prescriber signature			Dose							
Prescriber name (please print)										
Contact details				mg mg mg mg mg mg mg						
Pharmacy				Prescriber initials						
Comments			0800hrs Administrator initials							

Not to be administered

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

Date	Medicine Clozapine		Dose	X	X	X	25	25	50	75	100	100	100	125
Route	Frequency Evening	Prescriber to enter individual doses		mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg
Prescriber signature			Prescriber initials											
Prescriber name (please print)														
Contact details			2000hrs Administrator initials				AR	AR	RJ	ⓐ	CR	CR	AR	AR
Pharmacy			Pharmaceutical review											
Comments														

h. Bedford
Pager 2010
50 x 100mg 8/9

• 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.

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
Morning	12.5mg	25mg	25mg	25mg	25mg	25mg	25mg	25mg	50mg	50mg	50mg	50mg	50mg	50mg
Evening	X	X	X	25mg	25mg	50mg	75mg	100mg	100mg	100mg	125mg	125mg	125mg	150mg

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

Date	Medicine Clozapine	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Route Oral	Frequency Morning	Prescriber to enter individual doses	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Prescriber signature			[Signature]																	
Prescriber name (please print)			G. Gordon																	
Contact details			Nurse 2010																	
Pharmacy			[Signature]																	
Comments			Ceased 15/9/13. Patient started maintenance dose.																	
Date			15/9/13																	
Medicine			Clozapine																	
Dose			12.5	25	25	25	25	25	25	25	50	50	50	50	50	50	Ceased			
			mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg			
Prescriber initials			[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]	[initials]				
0800hrs Administrator initials			AR	AR	PJ	ST	ST	ST	CR	CR	AN	AN	ST	AR	AR	PJ				

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

Date	Medicine Clozapine		Dose		X	X	X	25	25	50	75	100	100	100	125
Route Oral	Frequency Evening	Prescriber to enter individual doses	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg
Prescriber signature 			Prescriber initials												
Prescriber name (please print) G. Bedford			2000hrs Administrator initials												
Contact details Pager 2010			Pharmacy												
Pharmacy 50 x 100mg 8/9			Pharmaceutical review												
Comments															

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

Prescriber initials											
2000hrs Administrator initials											
Pharmaceutical review											

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 blood results monitoring system		Recommended action
Green Range	WBC greater than $3.5 \times 10^9/L$ and Neutrophils greater than $2.0 \times 10^9/L$	Continue clozapine therapy.
Amber Range	WBC $3.0\text{--}3.5 \times 10^9/L$ or Neutrophils $1.5\text{--}2.0 \times 10^9/L$	Continue clozapine therapy with twice-weekly blood tests until return to 'green' range.
Red Range	WBC less than $3.0 \times 10^9/L$ or Neutrophils less than $1.5 \times 10^9/L$	Stop clozapine therapy immediately. Refer to local clozapine protocol for management guidelines.

• 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 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

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
														

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

Date	Medicine Clozapine		Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Route Oral	Frequency Morning	Prescriber to enter individual doses	Date day/month	1/9	2/9	3/9	4/9	5/9	6/9	7/9	8/9	9/9	10/9	11/9	12/9	13/9	14/9
Prescriber signature 			Dose	12.5	25	25	25	25	25	25	25	50	50	50	50	50	50
Prescriber name (please print) G. Bedford				mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg
Contact details Pager 2010			Prescriber initials														
Pharmacy M. Pugh			0800hrs Administrator initials	AR	AR	PJ	S.T.	S.T.	S.T.	CR	CR	AN	AN	ST	AR	AR	PJ
Comments																	

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	
<ul style="list-style-type: none">• Assess current smoking status• Review and document medical history, cardio-metabolic risk factors and drug interactions• Assess bowel habits, including presence of any unnecessary anticholinergic or other constipating agents• Provide and explain clozapine brochure to consumer and family/carer	<ul style="list-style-type: none">• Complete clozapine patient registration form and send to Clozapine Monitoring Centre. To be approved before prescribing• Inform your local clozapine coordinator• Provide pharmacist with blood test results and prescription• Complete high cost eligibility form• Complete clozapine baseline monitoring (see page 1)

5.2 Blood monitoring

All patients recommencing clozapine following an interruption in treatment must have a pre-treatment 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
<p>If clozapine dose missed for 72 hours or less:</p> <ul style="list-style-type: none">• Monitoring should continue as normal with no additional requirements <p>If clozapine dose missed for 72 hours but less than 4 weeks:</p> <ul style="list-style-type: none">• 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:<ul style="list-style-type: none">– 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 <p>If clozapine dose missed for 4 weeks:</p> <ul style="list-style-type: none">• 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.	
<input type="checkbox"/> First ever clozapine dose 1. Prior to clozapine dose take baseline temperature, pulse, respiration (TPR) and lying and standing blood pressure (BP) 2. Administer clozapine as prescribed 3. Repeat observations: <ul style="list-style-type: none">• every half an hour for 2 hours• every hour for 4 hours 4. If above observations are outside normal parameters, seek medical review	<input type="checkbox"/> Re-titration after treatment break (over 48 hours since last dose) 1. Prior to clozapine dose take baseline temperature, pulse, respiration (TPR) and lying and standing blood pressure (BP) 2. Administer clozapine as prescribed 3. Repeat observations: <ul style="list-style-type: none">• 30 minutes after dose then TWICE daily (default, unless alternate option completed below by Medical Officer)• minutes after dose then daily 4. If above observations are outside normal parameters, 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 [online](#) or using the '[blue card](#)' (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

Management 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 / Cardiomyopathy	Myocarditis – within 6–8 weeks of starting Cardiomyopathy – may occur at any time	Cease clozapine. Admit to hospital if myocarditis or cardiomyopathy is confirmed. 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 Very troublesome at night	Manage according to severity of symptoms. See literature for 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 exhaustive list of side effects. Please see product information for further advice.		

* **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 Guidelines².

Figure 24 below shows the suggested clozapine monitoring investigations

Clozapine monitoring (suggested guidelines only)*													
Investigations	(-) if required	Results										After 28 days	
		Baseline			Date (day 7): / /		Date (day 14): / /		Date (day 21): / /		Date (day 28): / /		
		Date completed	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal		Abnormal
Full blood count (FBC)	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Then continue weekly first 18 weeks then monthly	
White blood cell (WBC)	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Neutrophils	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Eosinophils	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Troponin – high sensitivity I or T	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Then at 6 weeks then 3 months. Then as per local protocol	
C-reactive protein (CRP)	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Electrocardiograph (ECG)	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Then continue as per local protocol	
Liver function test (LFT)	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>									
Urea and electrolytes (U&E)	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>									
Blood group	<input type="checkbox"/>												
Plasma glucose – fasting	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>								Then at 3 months then every 6 months	
Total cholesterol – fasting	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>									
Low density lipoprotein (LDL) – fasting	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>									
High density lipoprotein (HDL) – fasting	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>									
Triglycerides – fasting	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>									
Beta human chorionic gonadotropin (Beta HCG) – female	<input type="checkbox"/>		<input type="checkbox"/> +	<input type="checkbox"/> -								As required	
Cardiac ECHO	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>								Then continue as per local protocol	
Clozapine level (can help guide therapeutic dose)	<input type="checkbox"/>												
Full physical exam	<input type="checkbox"/>		<input type="checkbox"/>	<input type="checkbox"/>									
Height	<input type="checkbox"/>			m									
Weight	<input type="checkbox"/>			kg		kg		kg		kg		Then continue monthly	
Waist	<input type="checkbox"/>			cm							cm		
BMI [weight (kg)/height (m²)]	<input type="checkbox"/>												
Constipation	<input type="checkbox"/>		Check bowel habits daily for 4 weeks										Continue weekly
Smoking – cigarettes per day	<input type="checkbox"/>											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 $3.0\text{--}3.5 \times 10^9/L$, 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 $2.0 \times 10^9/L$ 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 $BMI = [weight\ (kg)/height\ (m^2)]$ where (kg) is a person's weight in kilograms and (m ²) 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
<p>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.</p> <p>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</p> <p>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.</p>

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.