

Prescribing and Monitoring Clozapine Treatment

1. Purpose and scope

This document provides information and resources to assist prescribers and other clinical staff to initiate clozapine treatment and to guide the subsequent monitoring requirements for patients prescribed clozapine.

Contents

1. Purpose and scope	1
2. Indications	2
3. Consent (see Appendix 1 for consent document)	2
4. Clozapine Registration (see Appendix 2A Clozaril® registration form)	2
5. Pre-treatment (see Appendix 3: Clozapine Pre-treatment Checklist)	3
6. Commencement of treatment (see Appendix 4)	3
6.1. Switching from another antipsychotic to clozapine:	3
6.2. Titration (See Appendix 5):	3
7. Monitoring	4
7.1. Blood counts:	4
7.2. Monitoring for myocarditis and cardiomyopathy:	5
7.3. Serum levels:	5
7.4. Assessment of adherence:	6
7.5. Other parameters of monitoring:	6
7.6. Bowel monitoring:	7
7.7. Interruptions in clozapine treatment: Dosage and blood monitoring requirements:	8
8. Withdrawal of treatment	8
8.1. Discontinuing treatment (Appendix 7 Discontinuation Notice):	8
8.2. Reasons for stopping clozapine:	8
8.3. Re-challenge:	9
9. Transfer of care of clozapine patient (appendices 8 and 9)	9
10. Definitions	9
11. Associated documents	9
12. References	10
Appendix 1 – Consent for Treatment with Clozapine	11
Appendix 2A – Patient Registration Form	12
Appendix 2B – Carelink Plus New User Registration Form for Healthcare Professionals	14
Appendix 3 – Pre-treatment Checklist	16
Appendix 4 – Commencement and maintenance of clozapine treatment	17
Appendix 5 - Clozapine titration regime	18
Appendix 6 – Porirua Protocol Flowchart	19
Appendix 7 – Discontinuation Notice	20
Appendix 8 – Notice of Transfer Form	22
Appendix 9 – GP Referral Letter	24
Appendix 10 - Clozapine Monograph	25
Appendix 11 - Clozapine Significant Side Effects and Management Advice	27

Prescribing and Monitoring Clozapine Treatment

2. Indications

Schizophrenia is the only currently registered indication. A closely related psychotic illness, schizoaffective disorder, is also sometimes treated with clozapine, subject to the same restrictions below. It's also suggested for Parkinson's related psychosis. One or both of the following features must also be present:

- Treatment resistance – defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotics each prescribed for an adequate duration. Adequate dose and duration are defined as antipsychotic drug trials of at least 6 weeks duration, including clinically judged compliance, with either
 - oral agents, at daily doses equivalent to at least 10mg/day haloperidol or 6mg/day risperidone (as tolerated), and/or
 - depot intramuscular antipsychotic agents, at comparable equivalent doses, of at least five depot intervals to establish a steady state (minimum three months).

OR

- Treatment intolerance – defined as the failure to achieve clinically effective doses of antipsychotic drug treatment due to intolerable adverse reactions. The trials of two different antipsychotics may be of shorter duration than six weeks if the individual could not tolerate either agent due to:
 - i) neuroleptic malignant syndrome (NMS), or
 - ii) severe extrapyramidal side-effects (pseudoparkinsonism, akathisia, dystonia, tardive dyskinesia), or
 - iii) other intolerable adverse effects (e.g. symptomatic hyperprolactinaemia).

3. Consent (see Appendix 1 for consent document)

The following must occur before treatment commences:

- Indications, possible adverse effects, monitoring procedures, and other treatment options should be fully discussed with the patient and family/caregivers (where available, and subject to health information privacy considerations). The discussion should be supplemented by written information.
(Note: guidance on health information sharing issues and involving family/whanau can be obtained from the Te Whatu Ora Waikato [Information Privacy policy](#) or the Privacy page of the intranet).

AND

- Consent should be obtained from the patient by the prescribing clinician wherever possible. The consent process and discussion of the above issues should be clearly documented in the clinical notes and using the consent to treatment form (Appendix 1).

OR

If the patient is judged incapable of giving informed consent:

- Next-of-kin, where available, should be involved in the consent process, AND
- A second opinion must be obtained from a psychiatrist approved by the Review Tribunal for the purposes of section 59 of the Mental Health Act, AND
- If not already in force, an application for compulsory treatment under the Mental Health Act must be made. Alternatively, a personal order providing for clozapine treatment, or the consent of an appointed welfare guardian.

Note: Clinicians should clearly document this alternative process, reasons for it, and discussion of the above issues in the clinical record.

4. Clozapine Registration (see Appendix 2A Clozaril® registration form)

- Due to the risk of agranulocytosis, patients must be registered with the clozapine supplier's national blood monitoring programme and database. This is intended to enhance haematological safety and to prevent patients from being re-exposed to clozapine if they had previously developed neutropenia or agranulocytosis.
- To enable this, a patient registration document needs to be completed at the conclusion of the pre-treatment process (detailed below) and sent to the supplier's blood monitoring system, with a copy sent to the pharmacy supplying clozapine. (Appendix 2A)
- When patients are registered in the national database, an acknowledgement is routinely sent to the prescribing clinician and should be recorded in the notes.
- Appendix 2B is for Carelink Plus New User Registration Form for Healthcare Professionals

Prescribing and Monitoring Clozapine Treatment

5. Pre-treatment (see Appendix 3: Clozapine Pre-treatment Checklist)

Following the decision by a psychiatrist (or by a psychiatric registrar in consultation with a supervising psychiatrist) to initiate clozapine, the following must be reviewed or arranged (also see Appendix 3).

- Baseline clinical assessment of function and symptoms, including HoNOS and GAF. Completion of additional rating scales is encouraged, e.g., PANSS, BPRS, GATES, AIMS.
- Medical history review with particular focus on seizures, constipation, cardiovascular disease and any haematological disorder. Family history of cardiovascular disease, especially prior to 50 years of age, is important to ascertain and document.
- Physical examination including abdominal examination, weight, height, pulse and blood pressure (lying and standing), temperature, waist circumference. Body mass index (BMI) should be calculated from measurements of weight and height (kg/m²). Pre-existing constipation should be assessed and adequately treated before clozapine initiation.
- An ECG is required within the four weeks prior to clozapine initiation. Any abnormalities (including QTc prolongation) should be considered in light of current drug treatment, and a risk-benefit analysis undertaken prior to initiation of clozapine. Specialist cardiology opinion may be required.
- Baseline echocardiogram -- if indicated by significant cardiac history (MI, heart failure, valvular disease) or abnormal ECG (other than prolonged QTc due to medication).
- A chest X-ray is required within the 6 months prior to initiation.
- Baseline complete blood count (CBC), electrolytes, renal and liver function tests, troponin-T, C-reactive protein (CRP), fasting blood glucose, HbA1c and lipid profile are also required, sampled no more than 10 days before initiation.
- Patients must be registered with the relevant national blood monitoring system prior to treatment initiation (see Section 4 above).
- General practitioners should be contacted regarding the decision to prescribe clozapine for any of their patients. Discussion should establish who will be responsible for cardiovascular, gastrointestinal, glycaemic and haematological monitoring (usually the psychiatrist); this should be documented in the notes, along with confirmation of who will manage emergent problems in any of these domains (usually the GP).

6. Commencement of treatment (see Appendix 4)

Given the level of care needed in the initial phase of treatment clozapine is recommended be commenced in an inpatient setting. Commencement in prison or in the community setting is not recommended. It will be very unusual for clozapine treatment to be commenced in a private setting.

6.1. Switching from another antipsychotic to clozapine:

Low to moderate potency first generation antipsychotics (such as chlorpromazine) have marked anticholinergic and sedative effects and lowering of the seizure threshold similar to clozapine. Combined treatment may lead to delirium or seizures.

All antipsychotics (including second generation agents) also carry a risk of agranulocytosis and should be used for as short a period as possible during the changeover.

Depot antipsychotics should not be administered after commencement of clozapine, which can occur on the day the depot is due.

6.2. Titration (See Appendix 5):

- Clozapine should be started with a small daily dose (12.5–25 mg) rising in graduated increments over two to three weeks until a good clinical response is seen or a dose of 300 mg/day is obtained.
- Further dose increases may be made according to clinical response. Maori and European patients generally require similar doses, while patients of Asian ethnicity may require slightly lower doses.
- The maximum recommended dose of 600mg/day is rarely needed although doses up to 900mg/day (the maximum licensed dose) can be given in exceptional cases.
- The risk of seizures is dose-dependent and rises substantially in doses over 600 mg/day. Clozapine serum level monitoring may be appropriate if non-compliance or toxicity are suspected, or occasionally if doses above 600 mg/day are prescribed.
- After stabilisation of the patient's clinical state, the dose of clozapine can often be tapered to a lower maintenance dose. Clozapine may be given as a single daily dose (usually in the evening) but divided doses may enhance tolerability, particularly with total daily doses above 200 mg/day.
- Pharmacies will not dispense clozapine unless patients are registered with a national monitoring system (see Section 4, above), AND

Prescribing and Monitoring Clozapine Treatment

- **Only** after complete blood counts are made available and screened by the pharmacy. Any deviations from white blood cell (WBC) and absolute neutrophil count (ANC) normal ranges will be reported to the clinician and treating team.

7. Monitoring

7.1. Blood counts:

Weekly CBCs are mandatory for the first 18 weeks. Thereafter CBCs are required at least monthly (once every 28 days) as long as treatment continues.

An immediate CBC must be performed:

- If signs or symptoms of infection occur. The patient should be regularly reminded to contact the treating doctor immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat, which may indicate neutropenia.

CBC monitoring should be continued at least twice weekly (Amber Alert Level):

- If an immediate CBC has been required, until a normal result is obtained.
- If the WBC shows a drop of $3.0 \times 10^9/L$ or more from baseline or a single drop of $3.0 \times 10^9/L$ or more.
- If the ANC falls to $(1.5-2.0) \times 10^9/L$, or there is a single drop of $3.0 \times 10^9/L$ or more.

Immediate discontinuation of clozapine (Red Alert Level) is required if:

- The WBC is less than $3.0 \times 10^9/L$ or the ANC count is less than $1.5 \times 10^9/L$.
 - Obtain daily blood tests to confirm and track the need to resume clozapine, and get a haematology consult with the full blood count history available to discuss.
 - Daily CBCs should be performed until haematological recovery has occurred and the patient must be closely monitored, especially for any signs of infection.
 - If WBC or ANC drop persists consult with a Haematologist regarding the use of filgrastim (GCSF).

General Cases:

	WBC $\times 10^9/L$	ANC $\times 10^9/L$
Amber	3.00-3.50	1.50-2.00
Red	<3.00	<1.50

Special cases of patients with persistently low WBC and/or low ANC counts:

Some patients show persistently low WBC and/or low ANC counts without any significant adverse effects, such as in patients with benign ethnic neutropenia, or chronic idiopathic neutropenia. In patients - with conditions such as these - who have no significant adverse effects, the Waikato Hospital haematology department have recommended the following cut off levels:

	WBC $\times 10^9/L$	ANC $\times 10^9/L$
Amber	2.00-3.50 (with approval*)	1.00-1.25 (with approval*)
Red	<2.00 (with approval*)	<1.00 (with approval*)

*Please refer to Haematologist for approval to continue with the revised cut-off levels. Mental Health Pharmacist to be notified.

Immediate discontinuation of clozapine (for other blood components) if:

- The eosinophil count rises above $3.0 \times 10^9/L$. Clozapine should only be restarted after the count is below $1.0 \times 10^9/L$.
- The platelet count falls below $50 \times 10^9/L$. Clozapine should not normally be reinitiated. However, if consideration is being given to reinitiate clozapine the patient's platelet count must be greater than $100 \times 10^9/L$, and a haematologist must be consulted. If a patient refuses a blood test at any stage and cannot be persuaded to reconsider, then clozapine must be discontinued and the patient's physical condition monitored for at least one month following discontinuation. Ideally the CBC should also continue to be monitored for a period of one month following discontinuation.

Prescribing and Monitoring Clozapine Treatment

Covid 19 and haematological changes: Data are emerging that show a reduction in WCC, neutrophils and lymphocytes in patients taking clozapine who become infected with COVID-19. This reduction is small (mean of around $1 \times 10^9/L$) and transient, recovering within 2 weeks.

- For some patients this temporary reduction in WCC and neutrophils may be sufficient to cause their blood tests to be classified as 'amber' or even 'red'. If clozapine-related neutropenia can be ruled out, it is not always necessary to stop clozapine for these patients. Stopping clozapine is very likely to cause a relapse in symptoms. Clozapine-related neutropenia can usually be ruled out if the neutropenia occurs in patients taking clozapine for more than six months, especially if more than a year. In addition, true clozapine related neutropenia follows a characteristic pattern of a precipitous fall in neutrophil counts of 'normal to nil' over a week or less.
- On the basis of our findings, clinicians should act to rule-out COVID-19 in patients presenting with a fall in neutrophil counts.

7.2. Monitoring for myocarditis and cardiomyopathy:

- Routinely add markers of inflammation (CRP or ESR) and cardiac muscle damage (troponin or CK) to the already mandated weekly routine bloods for first 4 weeks. CRP and troponin together are perhaps the best combination with regard to sensitivity and specificity.
- Routinely monitor vital signs including temperature on the day of blood tests, particularly for the first 4 weeks
- Obtain ECG and cardiac enzymes as soon as clinical concerns for myocarditis arise. If a recent, pre-symptomatic baseline ECG is on file, ECG changes can be better interpreted.
- Clozapine patients who develop fever, tachycardia (new onset or worsening), shortness of breath (at rest or on exertion), chest pain, palpitations, unexplained fatigue, ECG changes, arrhythmias or any other symptoms of heart failure should be investigated promptly. This includes a medical assessment, CBC, and consider testing for cardiac biomarkers (including BNP, troponin-T and CRP).
- Pay attention to any rise in eosinophil count after the high-risk period which may indicate subclinical myocarditis.
- Echocardiography should be performed, in consultation with a cardiologist, if elevations of cardiac inflammatory markers are detected.
- Rapid or severe deterioration warrants immediate hospitalisation for assessment.
- If myocarditis or cardiomyopathy is suspected, referral to cardiac specialists must be undertaken immediately. Ongoing administration of clozapine should be discussed with the cardiology team.
- In all cases referral should include an ECG, chest X-ray and an echocardiogram request. The referral must clearly identify that the person is being treated with clozapine.

Covid-19 vaccination and myocarditis and pericarditis

- A small increased risk of pericarditis and/or myocarditis has been observed in people who have received an mRNA COVID-19 vaccine (including Comirnaty (Pfizer) and Spikevax (Moderna), compared to unvaccinated people.
- COVID-19 itself is associated with a substantially higher risk of myocarditis and other cardiac complications compared with vaccination.
- Pericarditis and myocarditis after mRNA COVID-19 vaccines have been reported most commonly in males under 30 years of age, and most commonly after the second vaccine dose. Most myocarditis and pericarditis linked to mRNA vaccination has been mild and patients have recovered quickly. Longer-term follow-up is ongoing.
- Symptoms of myocarditis or pericarditis typically appear within 1-5 days of an mRNA vaccine dose and may include chest pain, palpitations (irregular heartbeat), syncope (fainting) or shortness of breath. People who experience any of these symptoms after having an mRNA COVID-19 vaccine should seek prompt medical attention.
- Initial investigations should include ECG and blood troponin levels. A chest X-ray, and other investigations for other differential diagnoses should be undertaken as clinically indicated.
- Future vaccine dose recommendations vary depending on investigation results.

7.3. Serum levels:

Patients show considerable variability in clozapine serum concentrations due to dose and to biological differences in absorption and metabolism. Studies indicate an inconsistent relationship between serum levels and clinical response. Clozapine serum levels should thus be performed only for a specific purpose and should NOT be performed routinely. The situations in which it may be useful to consider clozapine serum level testing include:

- Poor clinical response despite adequate dosage.
- Signs of toxicity at therapeutic doses, e.g. excessive sedation, hypersalivation or constipation, seizures.

Prescribing and Monitoring Clozapine Treatment

- Concomitant medications or substances that may affect the metabolism and serum level of clozapine, e.g. change in tobacco smoking or caffeine consumption.
 - By-products of tobacco smoking, particularly polycyclic aromatic hydrocarbons, are metabolic inducers of cytochrome P450 1A2, which increases clozapine metabolism thereby lowering clozapine serum levels. This requires an increased dose of clozapine for the same therapeutic effect.
 - Likewise when a patient reduces or quits smoking, clozapine levels typically rise due to normalisation of CYP 1A2, and clozapine dose will need to be reduced. This scenario warrants review and sometimes monitoring of clozapine serum level.
 - Caffeine is a competitive substrate for CYP1A2 thus displacing clozapine and raising levels. This is one reason why decaffeinated coffee has become the norm in the inpatient setting. Discharged patients who resume regular coffee consumption likewise warrant review and may require clozapine level monitoring.
- Co-morbid medical disorders, especially with hepatic impairment.
- There has been case reports of Covid-19 Infection affecting clozapine serum levels. Case studies indicate that coronavirus disease 2019 (COVID-19) can be associated with toxic clozapine levels, requiring monitoring to maintain therapeutic levels and prevent relapses of psychosis.^{1–4} High clozapine levels are consistent with infection-related inflammation inhibiting cytochrome P450 1A2 (CYP1A2) and slowing clozapine metabolism.⁵
- Suspected non-adherence.
Serum clozapine levels over 2000 nmol/L appear associated with an increased risk of neurological effects. In such circumstances, the clozapine dose may be adjusted to maintain a serum level within the usual therapeutic range (1050 – 1800 nmol/L) if the patient's clinical condition permits. Sampling is best done between 10-16 hours following last dose, ideally 12 hours.

7.4. Assessment of adherence:

It may be worth taking serum levels on different days to the CBC; this may be more likely to detect non-adherence if the patient only adheres when they know a blood test is due.

Total non-adherence is easy to diagnose as both clozapine and N-desmethylozapine levels will be low or non-existent. Conversely, serum clozapine and N-desmethylozapine levels within the expected ranges do not guarantee adherence for more than a week or so.

Partial adherence is difficult to detect. If the clozapine level is congruent with previous results but the N-desmethylozapine level is relatively low, this may indicate recent adherence but longer term partial or non-adherence.

7.5. Other parameters of monitoring:

Appropriate interventions should be made if any of the following are found to be abnormal:

- Daily recordings of pulse and blood pressure** (both lying and standing), temperature and bowel movements are recommended during the dose titration period. Thereafter these observations should be recorded as required due to adverse effects or a change of dose.
- Weight, height, waist and hip circumference** should be measured, and Body Mass Index (BMI) and waist/hip ratio calculated at baseline and monitored regularly.
- Fasting blood glucose levels** and HbA1c are recommended at baseline and three months after starting treatment, then at six months and annually thereafter (or more frequently if clinically indicated). For people at high risk of developing diabetes monitor monthly for three months, then every three months for the first year, then every six months thereafter.
- A fasting lipid screen** is recommended at baseline and then three months, then at six months and then annually (or more frequently if clinically indicated). For people at high risk monitor monthly for three months, then every three months for the first year, then every six months thereafter.
- Liver function tests** are recommended to be assessed at baseline, three months and six months after starting treatment and then annually (or more frequently if clinically indicated).
- An ECG** should be monitored annually. Anyone with ECG changes should be investigated.
- Myocarditis /cardiomyopathy** occurs rarely in the first few months of treatment and very rarely later in treatment. Myocarditis has a very rapid onset and there are no screening tests of proven value, indeed these can lead to a false sense of reassurance. Effective monitoring for these serious complications is heavily reliant on careful clinical vigilance.
 - There are few reports of Covid 19 associated myocarditis - occur predominantly in adolescents and young adults, more often in males than females, more often after the second dose of the vaccine, and typically within 4 days after vaccination [1]. Most cases appeared to be mild and follow up is ongoing.
 - Anyone who develops fever, tachycardia (new onset or worsening), shortness of breath (at rest or on exertion), chest pain, palpitations, unexplained fatigue, ECG changes, arrhythmias or any other symptoms of heart failure should be

Prescribing and Monitoring Clozapine Treatment

investigated promptly. This includes a medical assessment, FBC, and consider testing cardiac biomarkers (including BNP, troponin-T and CRP).

- Baseline echocardiogram -- if indicated by significant cardiac history (MI, heart failure, valvular disease) or abnormal ECG (other than prolonged QTc attributed to medication).
- Rapid or severe deterioration warrants immediate hospitalisation for assessment.
- If myocarditis or cardiomyopathy is suspected referral to cardiac specialists must be undertaken immediately. Ongoing use of clozapine should be discussed with the cardiology team.
- In all cases referral should include an ECG, chest X-ray and an echocardiogram request. The referral must clearly identify that the person is being treated with clozapine.

7.6. Bowel monitoring:

Constipation is a common problem in people taking clozapine. Clozapine can cause gastrointestinal hypomotility throughout the entire digestive system from oesophagus to rectum; the resulting effects can include dysphagia, delayed gastric emptying, bowel obstruction, ischaemia, megacolon and perforation leading to peritonitis. The mechanism is likely due to clozapine's potent antimuscarinic and antiserotonergic activity which inhibit intestinal smooth muscle contraction, resulting in delayed transit, reduced gastrocolic reflexes, and reduced intestinal sensitivity to distension. This is a particular concern when other constipating medications with anticholinergic activity (benztropine, procyclidine, tricyclic antidepressants) or opiates are co-prescribed.

Life-threatening bowel complications have been associated with clozapine use. People may present acutely unwell with an ischaemic, distended bowel. The bowel is normally close to perforation or this has already occurred. Systemic signs of peritonitis or sepsis may be present. Whilst perforation is uncommon, mortality rates are high and more deaths have occurred in New Zealand from this complication than from agranulocytosis. Risk factors include higher doses of clozapine (and subsequently higher plasma levels); co-morbid medical illness and fever (inhibiting clozapine metabolism and increasing plasma levels); co-administration of medications that inhibit CYP1A2, increasing clozapine plasma levels; and the first four months of treatment may be a particularly vulnerable time with 36% of cases occurring then. The most consistently reported presenting signs and symptoms are moderate/severe abdominal pain, abdominal distension, and vomiting. If a person presents with these symptoms urgent surgical (or medical) referral and treatment is required. Clozapine treatment should be reduced or withheld.

Constipation should be assessed on an ongoing basis and treated to ensure it has resolved adequately. Bowel movement monitoring is essential in the early phase of treatment.

The Porirua Protocol (Appendix 6)

- The Porirua protocol is a regimen of laxatives for the prevention and treatment of clozapine-related constipation that was first published in 2014 by researchers at the University of Otago, Wellington. The protocol primarily uses docusate sodium with sennoside B, with an additional laxative for patients with resistant constipation. A small study of 14 patients taking clozapine found that the Porirua protocol reduced the average time for material to pass along the colon by two days. *
 - When clozapine is initiated, patients should be concurrently prescribed two tablets of docusate sodium with sennoside B each night to prevent the onset of constipation.
 - If the patient has not had a bowel movement for two days, increase the dose of docusate sodium with sennoside B by one tablet in the morning and review the patient within 48 hours.
 - If still constipated, increase the dose again by one tablet in the morning and review the patient within 48 hours.
 - If the patient remains constipated, a rectal examination should be performed to exclude impaction:
 - If impacted, docusate sodium with sennoside B should be stopped and the patient discussed with a psychiatrist or gastroenterologist; manual dis-impaction and enemata may be required
 - If not impacted, continue with two tablets of docusate sodium with sennoside B, twice daily, and review after 48 hours.
 - If constipation persists, add one macrogol sachet, twice daily, and review after 48 hours.
 - If constipation is ongoing the patient should be discussed with a gastroenterologist.
- * If the patient develops diarrhoea it may be appropriate to reduce the dose or withdraw laxative treatment; close monitoring is essential.
- Red flags for constipation in clozapine patients requiring urgent medical review:
 - Moderate to severe abdominal pain which lasts for more than one hour
 - Any abdominal pain or discomfort which lasts for more than one hour and one or more of:
 - Abdominal distension
 - Diarrhoea, especially if bloody
 - Vomiting

Prescribing and Monitoring Clozapine Treatment

- Absent or high-pitched bowel sounds
- Haemodynamic instability
- An elevated white blood cell count
- Metabolic acidosis
- Additional signs of sepsis

7.7. Interruptions in clozapine treatment: Dosage and blood monitoring requirements:

Period of interruption	Dosage & blood monitoring requirements
2 days or less (48 hours)	No change to dosage or blood monitoring requirements.
3 days (72 hours)	Start on 12.5mg and titrate up. Maintain current blood monitoring.
>3 days but <4 weeks	Start on 12.5mg and titrate up. For patients on monthly CBC monitoring: Weekly monitoring for 6 weeks. If no abnormality, resume monthly blood monitoring. For patients on weekly CBC monitoring: continue weekly blood monitoring for 6 weeks or as long as needed to reach 18 weeks. Notify clozapine clinical support technician (0800 535 020 or carelinkplus@viatris.com) to ensure national database system is updated.
> 4 weeks	New Patient registration form required A new pre-treatment blood result and blood monitoring as for new patients (weekly for 18 weeks). Start on 12.5mg/day and titrate up.

8. Withdrawal of treatment

8.1. Discontinuing treatment (Appendix 7 Discontinuation Notice):

If clozapine treatment is to be discontinued, where possible the dose should be gradually reduced to avoid rebound exacerbation of psychotic symptoms or cholinergic rebound.

If abrupt discontinuation is necessary, the person should be closely monitored for a period of two to three weeks for rebound psychosis. An anticholinergic medication may be required to manage cholinergic symptoms on withdrawal.

As noted above, the CBC should be monitored for a period of one month following cessation of clozapine treatment (at weekly intervals if the patient is on weekly monitoring, or one further CBC at one month if the patient is on monthly monitoring).

8.2. Reasons for stopping clozapine:

1. Haematological factors (drop in WBC or ANC as per guideline)
2. Other severe adverse effects (e.g. suspicion of cardiotoxicity, uncontrolled seizures, neuroleptic malignant syndrome, severe sedation, intolerable hypersalivation, severe constipation).
3. No improvement (reflected in HoNOS or GAF) with adequate clozapine serum level (above 1000nmol/L) over a minimum period of six months. Augmentation strategies may be considered.
4. Withdrawal of consent if not under the Mental Health Act.
5. Persisting non-compliance with treatment or monitoring despite reasonable attempts to ensure this.

Should treatment be withdrawn for any reason, the relevant pharmaceutical company (for Te Whatu Ora Waikato, Mylan) must be informed of the date and reason for discontinuation so that the monitoring database can be updated.

Prescribing and Monitoring Clozapine Treatment

8.3. Re-challenge:

- For those whose clozapine is discontinued because of agranulocytosis, clozapine must not be reinitiated at any time.
- For those whose clozapine is discontinued because of neutropaenia, clozapine must only be reinitiated after consultation with a haematologist and the relevant national monitoring system.
- Clozapine re-challenge may be considered for some patients who have experienced previous severe adverse effects (e.g. haematological or cardiotoxicity).
- This should be carefully discussed with appropriate specialists and the risks, benefits and alternatives documented and discussed with the patient, family/whanau and other caregivers as appropriate.
- To be considered after full clinical resolution of the toxicity and, in the case of cardiac adverse effects, lack of evidence of residual functional impairment.
- Under closely controlled conditions, initially typically in hospital and restarting with low, slowly increased doses.
- Frequently repeated assays of laboratory and cardiac markers that had been abnormal during acute myocarditis is mandatory; these patients typically require close inpatient monitoring.

9. Transfer of care of clozapine patient (appendices 8 and 9)

Complete and send the documents in appendices 8 and 9 when a patient prescribed clozapine is transferring into the community or to another hospital/care facility

10. Definitions

AIMS	Abnormal Involuntary Movement Scale
ANC	Absolute Neutrophil Count
BPRS	Brief Psychiatric Rating Scale
CRP	C-Reactive Protein
CK	Creatine Kinase
ESR	Erythrocyte Sedimentation Rate
CBC	Complete Blood Count
GAF	Global Assessment of Function
GATES	General Akathisia Tardive phenomena & Extrapyrmidal rating Schedule
HoNOS	Health of the Nation Outcome Scale
PANSS	Positive and Negative Syndrome Scale
WBC	White Blood Cell

11. Associated documents

- Mental Health (Compulsory Assessment and Treatment) Act 1992
- Protection of Personal and Property Rights Act 1988.
- Clozaril®, Viatris Ltd. Medsafe data sheet 13 March 2023
- Clopine®, Douglas Pharmaceuticals Ltd. Medsafe data sheet 29 July 2021.
- ClopineConnect® Resource Folder
- Clozaril® Resource Folder 2010

Prescribing and Monitoring Clozapine Treatment

12. References

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4. Menkes DB, et al. (2017). Steady-State Clozapine and Norclozapine Pharmacokinetics in Maori and European Patients. EBioMedicine. doi:10.1016/j.ebiom.2017.11.030
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7. Guidance on Myocarditis and Pericarditis after mRNA COVID-19 Vaccines by Australian Technical Advisory Group on Immunisation (ATAGI), the Cardiac Society of Australia and New Zealand (CSANZ), the Royal Australian College of General Practitioners (RACGP), the Australian College of Rural and Remote Medicine (ACRRM), the Australasian College for Emergency Medicine (ACEM) and the Paediatric Research in Emergency Departments International Collaborative (PREDICT). Updated 8 November 2021
8. Consensus statement on the use of clozapine during the COVID-19 pandemic
Dan Siskind, William G. Honer, Scott Clark, Christoph U. Correll, Alkomiet Hasan, Oliver Howes, John M. Kane, Deanna L. Kelly, Robert Laitman, Jimmy Lee, James H. MacCabe, Nick Myles, Jimmi Nielsen, Peter F. Schulte, David Taylor, Helene Verdoux, Amanda Wheeler and Oliver Freudenreich
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10. MEDSAFE Safety Information Alert Communication-Important updates to clozapine data sheets and monitoring during covid-19 pandemic. Published: 9 June 2020 Revised: 6 November 2020

Document Ownership

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Prescribing and Monitoring Clozapine Treatment

Appendix 1 – Consent for Treatment with Clozapine

CONSENT FOR TREATMENT WITH CLOZAPINE

Clozapine (trade name “Clozaril”) is an antipsychotic medicine used to treat disturbances of thinking which occur in schizophrenia and related psychoses.

Advantages of clozapine:

1. Clozapine is an effective medicine for schizophrenia. It may help some people who have not been helped by other antipsychotic medicines. It may also help treat some symptoms that are not helped by other medicines.
2. Clozapine is much less likely than other similar medicines to cause side effects such as stiffness, unusual movements or restlessness. In particular, clozapine is not known to cause tardive dyskinesia. This is a condition which involves unwanted movements of the tongue, mouth, face or limbs. It may occur with long-term use of some other medicines used in schizophrenia.

Disadvantages of clozapine:

1. Clozapine can cause serious side effects in a few people. These include:

- A decrease in the number of white blood cells which fight infection.

This can lead to serious or even fatal infections if it is severe and not treated quickly. To decrease the risk of this reaction being severe, it is necessary to have frequent blood tests while taking clozapine. This will mean having a blood test at least once a week for the first 18 weeks of treatment, then at least every four weeks thereafter. Extra blood tests may be required at any sign of infection i.e. sore throat or fever.

- Constipation is common and can be serious. If it occurs, report this to your nurse or doctor
- Possible increased risk of diabetes or metabolic syndrome
- Seizures or fits. These are more likely to occur when taking higher doses of clozapine. If it occurs, report this to your nurse or doctor
- Myocarditis (inflammation of heart muscle) or cardiomyopathy are rare adverse effects

2. Other side effects are less serious but may be unpleasant for some people. The more common ones include drowsiness, fast heart rate, weight gain, increased saliva, and dizziness.

In order to lessen the risk of a serious reaction to clozapine, blood test results are checked by the pharmacist before they can dispense clozapine. These results are also shared with the pharmaceutical company that supplies clozapine – Mylan - together with your name, sex, age, doctor's name, pharmacy name. All agencies are bound to keep this information confidential.

Statement of Service User/Tangata Whaiora

I have had the benefits and drawbacks explained to me concerning clozapine treatment. I understand the above information and realize that clozapine may help me but may also lead to serious side effects. I agree that while I am taking this medicine I will have blood tests when asked by my doctor or other staff.

Service user /Tangata Whaiora name..... Date of birth.....

Signature Date

Next Of Kin

Have next of kin been informed or been part of the treatment discussions? Yes ☐ No ☐

If yes, who?:

If no, what were the reasons?

Statement of Witness

I have discussed this consent form with this service user/Tangata Whaiora and next of kin (if applicable) and am satisfied that they fully understand it and their consent is freely given.

Name: Position:.....

Signature: Date

Prescribing and Monitoring Clozapine Treatment

Appendix 2A – Patient Registration Form

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Patient Registration

Please return to Viatris Limited PRIOR to commencing *Clozaril* treatment

► By Email: carelinkplus@viatris.com

Patient Family Name _____

First Name(s) _____

Date of Birth ____/____/____ NHI Number _____ Sex ☐ M ☐ F

Dispensing Pharmacy _____

Laboratory _____

Consultant _____ Email _____

Mental Health Unit/Team _____

Phone Number _____

Pre-treatment baseline WBC and Neutrophils

Date: ____/____/____

White Blood Count _____ x10⁹/L Neutrophils (absolute) _____ x10⁹/L

Treatment start date: ____/____/____

The pretreatment baseline WBC and Neutrophil counts must be from a blood sample taken no more than 10 days before starting *Clozaril* treatment. These should be in the normal range.

Statement

"I am a medical practitioner registered by the Medical Council of New Zealand in the scope of practice of psychiatry. I confirm that I have explained to the patient the purpose of the Viatris CareLink Plus Database ('Database') and that:

- (a) patient name, gender, Date of Birth, NHI number, *Clozaril* treatment dates and dose(s) will be stored in the Database
- (b) following every blood test the patient's white blood count and neutrophils will be provided to Viatris Limited, New Zealand by the testing laboratory and stored in the Database
- (c) health professionals and dispensing pharmacies will have access to such information
- (d) the patient will be entitled to access such information

I also confirm on behalf of the patient that the collection, storage, use and disclosure of such information has been authorised by, or on behalf of, the patient."

Print Name: _____ Signature: _____

Date: ____/____/____ Consultant ☐ Registrar (on behalf of consultant) ☐

Prescribing and Monitoring Clozapine Treatment

Appendix 2A – Patient Registration Form (continued)

Privacy Statement: Viatris Limited ('Viatris New Zealand') collects and holds, uses, and discloses personal information, such as name and contact details of patients and healthcare professionals ('HCPs') and the health information of patients, for the purpose of operating and administering the *Clozaril* patient blood monitoring program ('Program') for participating patients on the Carelink Plus database ('Database'). This includes registering HCPs and patients on the Database, storing patients' blood tests, monitoring patients' use of the products, communicating with HCPs and patients about the products to support the administration and use of the products, complying with regulatory obligations (including the reporting and processing of adverse events patients may experience), and sending invitations to participate or arranging for participation in activities managed by or on behalf of Viatris New Zealand. Viatris New Zealand may need to disclose this personal information to its third party services providers and affiliates, who may be located overseas, for these purposes, and personal information in the Database is held on Viatris New Zealand's behalf in servers located overseas in the UK and/or Ireland. By providing your personal information to Viatris New Zealand, you agree that you understand this Privacy Statement. If you are an HCP, you consent to Viatris communicating with you to facilitate the transmittal of invitations to participate or arranging to participate in activities managed by or on behalf of Viatris New Zealand. Viatris is committed to patient safety. In accordance with regulatory obligations, Viatris has a systematic process in place to collect, store, and process reports of adverse events experienced by patients taking a Viatris product, when identified by a Viatris representative (or by a third party acting on behalf of Viatris). All information forwarded to the Viatris drug safety department is treated in accordance with local privacy laws and may be captured and processed in countries outside of the jurisdiction in which it was collected, and shared with health authorities or other pharmaceutical companies with whom Viatris has a license agreement for the purpose of meeting the regulatory requirements for reporting safety information on Viatris products. Viatris drug safety department may contact the patient's HCP to collect further information on the adverse event. You are not obliged to provide personal information. However, if you do not provide information you may not, for example, be able to participate fully in activities managed by us. You have the right to access, update or correct your personal information and/or decline to receive communications from Viatris. To find out how, please refer to our: Privacy Policy <https://www.viatris.com/en-nz/im/new-zealand/viatris-privacy-notice> or contact Viatris New Zealand, PO Box R1462, Royal Exchange Post Office, NSW, Australia 1225. Email: dataprivacy.JANZ@viatris.com

***Clozaril* (clozapine) 25 milligrams, 100 milligrams tablets.** Prescription Medicine. Indicated for treatment-resistant schizophrenia in adult patients. Review the datasheet (available from www.medsafe.govt.nz) for information on dosage, contraindications, precautions, interactions, and adverse effects. Prescriber restrictions apply. Persons prescribing clozapine must comply with appropriate local treatment guidelines. *Clozaril* is a Viatris company trademark. Copyright© 2022 Viatris Inc. All rights reserved. Viatris Limited, Auckland. Ph 0800 579 811. CLZ-2022-0110. TAPS DA2211RY-0703. Last updated August 2022.

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Appendix 2B – CareLink Plus New User Registration Form for Healthcare Professionals

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CareLink Plus New User Registration

It is mandatory to complete all sections of this form. This document is a statement of intent from a Healthcare Professional, Mental Health Centre or Pharmacy to participate in the blood monitoring programme for *Clozaril* Patients in association with CareLink Plus - CLOZARIL PATIENT MONITORING SYSTEM (CPMS).
Email: carelinkplus@viatris.com

Title: _____

Given Name: _____ Surname: _____

Designation: _____

Mental Health Unit/Pharmacy: _____

Address: _____

Post Code: _____ DHB: _____

Phone: _____ Email: _____

I understand and agree to the conditions of the blood monitoring programme for *Clozaril* Patients as outlined in the *Clozaril* Data Sheet, which I have read. I also agree to have my contact details made available to other Health Care Professionals for the purposes of assisting patients with their blood monitoring.

Signature: _____ Date: ____/____/____

Approved by MHU/Pharmacy Manager/Clinical Director: Name: _____

Signature: _____ Date: ____/____/____

By completing and submitting this registration form by email, you will be registered to access CareLink Plus. The CareLink Plus technician will contact you shortly with your login details.

NB. This information is treated confidentially and used only to update CareLink Plus.

Prescribing and Monitoring Clozapine Treatment

Appendix 2B – Carelink Plus New User Registration Form for Healthcare Professionals (continued)

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Prescribing and Monitoring Clozapine Treatment

Appendix 3 – Pre-treatment Checklist

A - Clozapine therapy pre initiation checklist

	Process	Dr/RN sign	Date
A1	The patient has been adequately informed about the rationale to initiate clozapine treatment	Dr	
A2	The clinical benefits and potential risks involved have been clearly highlighted	Dr	
A3	The patient and caregiver have been well informed of the two prerequisites: a) compliance with clozapine treatment b) adherence to blood monitoring programme as two conditions upon which the decision to prescribe clozapine rests.	Dr	
A4	Is the patient on medications that risk suppression of bone marrow eg carbamazepine, sulphonamides, trimethoprim? Clozapine should not be prescribed with these medicines.	Yes/No (circle) Dr	
A5	The patient has signed the consent form	Dr	
A5	The following measurements have been completed and documented <ul style="list-style-type: none"> • Weight and BMI • Baseline complete blood count (CBC), (cannot be earlier than 7 days prior to initiation of clozapine treatment) Please use Mylan blood request forms so that results will be sent to CarelinkPlus Database and relevant Pharmacy) • Liver function test (LFT) • Urea and electrolytes (U&Es) • Fasting blood glucose • HbA1c • Fasting lipid profile • B-type natriuretic peptide (BNP) • C-reactive protein • Troponin T • Blood pressure (lying and standing), temperature and pulse rate • Baseline ECG • Baseline chest X ray (within 6 months prior to initiation) • Baseline echocardiogram - if indicated by significant cardiac history (MI, heart failure, valvular disease) or abnormal ECG (other than prolonged QTc) 		
A6	The clozapine patient registration form has been completed and forwarded to Mylan CarelinkPlus for registration prior to initiation of treatment. A copy to be faxed to the Pharmacy supplying the clozapine.(The registration form is available in the guidelines and the clozapine resource folder)		
A7	A copy of the registration form has been included in the patient's Clozapine folder		

Prescribing and Monitoring Clozapine Treatment

Appendix 4 – Commencement and maintenance of clozapine treatment

Clozapine initiation and maintenance treatment checklist

	Checklist	Sign	Date
B1	Where complete withdrawal of existing conventional antipsychotic treatment is not practicable, a cross-tapering regimen is in place with the current antipsychotic while clozapine is slowly built up to an adequate dose.	Dr	
B2	The dose titration is appropriate and according to guidelines and the titration chart.	Dr	
B3	The rate of dose increase is guided by the level of patient tolerance and the co-existence of any other physical conditions.	Dr	
B4	The patient's relevant physical symptoms will be closely monitored e.g. flu-like symptoms, sore throat etc	RN	
B5	Close monitoring and/or observation for adverse reactions, particularly risk of seizures, are in place.	RN	
B6	Weekly CBC (white blood count and differential) is being performed for the first 18 weeks of treatment. Week 1 ____/____/____ Week 18 ____/____/____	Dr to order. RN	
B7	Liver function tests (LFTs) checked one month following initiation of treatment, then at 3 months and 6 monthly thereafter unless there are clinical indications for more frequent liver function testing. Week 4 ____/____/____ 3 months ____/____/____ 6 months ____/____/____	Dr to order. RN	
B8	Temperature, blood pressure and pulse is being measured and recorded at least once daily during the first two weeks of treatment . (Monitoring of physical signs might need to be performed more frequently or for longer than two weeks if any abnormalities are detected during the treatment process.)	RN	
B9	ECG monitored when indicated and if so when was it performed. ____/____/____	Dr to order.	
B10	Blood glucose levels and HbA1c performed at 3 months, then at 6 months or more frequently if clinically indicated (fasting preferable). 3 months ____/____/____ 6 months ____/____/____	Dr to order. RN	
B11	The frequency of CBC monitoring has been reduced to 4 weekly intervals (provided that no abnormalities were detected after the initial 18 week period.) 4 weekly start date ____/____/____ Four weekly monitoring must remain in place as long as clozapine treatment continues. More frequent monitoring however is required, e.g. weekly or fortnightly whenever blood tests indicate abnormal results.	Dr to order RN	

Prescribing and Monitoring Clozapine Treatment

Appendix 5 - Clozapine titration regime

The Medsafe datasheet recommends an initial starting dose of 12.5 mg with gradual increments to achieve a total daily dose of 300mg in 14-21 days. One example of dose titration is illustrated below.

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

Higher doses may be given in the evening if drowsiness during the day is a problem. It is recommended that no more than 200mg is given as the night dose during the early titration phase. An alternative regimen may look something like this

DAY	AM DOSE (mg)	PM DOSE (mg)
1		12.5
2	12.5	12.5
3	25	25
4	25	25
5	25	75
6	25	75
7	50	100
8	50	100
9	75	125
10	75	125
11	100	150
12	100	150
13	100	200
14	100	200

After achieving a total daily dose of 300mg it is recommended that further increments be limited to 50-100mg with a maximum of 2 increases per week. Extra caution is needed in the elderly, and where there is renal, hepatic or cardiovascular impairment. For these patients the dose starts at 12.5mg daily and is increased more slowly, no more than 25mg at a time. Such cases generally require lower maintenance doses. Patients/Tangata Whaiora with a history of epileptic seizures also require extra care.

Prescribing and Monitoring Clozapine Treatment

Appendix 6 – Porirua Protocol Flowchart

PORIRUA PROTOCOL for all clozapine treated patients

- Guidance to prevent clozapine-related constipation -

RED FLAGS

Urgent medical review required for the following:

- Moderate to severe abdominal pain lasting over an hour
OR
- Any abdominal pain/discomfort lasting over an hour AND one or more of the following: abdominal distension; diarrhea (esp bloody); vomiting; absent or high pitched bowel sounds; metabolic acidosis; hemodynamic instability; leukocytosis or other signs of sepsis

1

1. Start regular docusate & senna 2 tabs nocte
 2. Be alert for **RED FLAGS** which might suggest serious pathology
 3. Monitor bowel function regularly
- Be aware patients under-report constipation symptoms
For monitoring consider using Bristol Stool Chart

If still constipated

2

Review within 48 hours

Increase docusate & senna by one tab every 2 days until no longer constipated or max of 2 tabs bd reached

If still constipated

3

Review within 48 hours

- Rectal examination to exclude impaction
- a) If impacted stop docusate and senna
 - b) If not impacted continue docusate & senna 2 tabs bd
- Discuss with expert (may need enemas, manual disimpaction)

If still constipated

4

Review within 48 hours

Add macrogol 1 sachet bd

If still constipated

5

Review within 48 hours

Discuss with expert for formulation of individualized regime (may include increased dose of macrogol and enemas)

If bowel function satisfactory
Continue treatment and monitoring

If diarrhea develops
Gradually reverse steps. Reduce then stop any macrogol. Reduce docusate & senna by one tab every 2 days until bowel function satisfactory
Continue treatment and monitoring

Prescribing and Monitoring Clozapine Treatment

Appendix 7 – Discontinuation Notice

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Notice of Discontinuation of Clozaril® (clozapine) therapy

Name of Patient _____

NHI Number _____ Date of Birth ____/____/____

Mental Health Unit _____

Prescribing Consultant/Registrar _____

Date Clozaril Treatment Discontinued ____/____/____ Last Clozaril tablet daily dose ____/____/____

Other Medications _____

Reason for Discontinuation:

☐ Non-Compliance with; Medication ☐ Blood Tests ☐

☐ Lack of Efficacy – i.e. the patient received adequate doses of Clozaril tablets or an adequate period of time to assess the clinical efficacy of Clozaril therapy

☐ Adverse Drug Event (please describe) _____

Was the adverse event considered to be related to Clozaril treatment? Yes ☐ No ☐

☐ Death (please provide cause of death) _____

Was the patient's death considered to be related to Clozaril treatment? Yes ☐ No ☐

☐ Other (please specify) _____

Name _____

Signature _____ Date ____/____/____

Please complete and forward this form to CareLink Plus.

Email	Post	Phone
carelinkplus@vhi.co.nz	PO Box 11183 Ellerslie Auckland 1542	0800 535 020

NB. This information is treated as confidential and used to update CareLink Plus.

Prescribing and Monitoring Clozapine Treatment

Appendix 7 – Discontinuation Notice (continued)

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Prescribing and Monitoring Clozapine Treatment

Appendix 8 – Notice of Transfer Form

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Notice of Transfer of a patient
on Clozaril® (clozapine) therapy

Name of Patient _____

NHI Number _____ Date of Birth ____ / ____ / ____

Transferred to (Service) _____

Transferred to (Doctor) _____

Date of Transfer ____ / ____ / ____

Comments: _____

Name of the Person Completing this Form: _____

Please complete and forward this form to CareLink Plus.

Email

carelinkplus@viatris.com

Post

PO Box 11183
Ellerslie
Auckland 1542

Phone

0800 535 020

NB. This information is treated as confidential and used to update CareLink Plus.

Prescribing and Monitoring Clozapine Treatment

Appendix 8 – Notice of Transfer Form (continued)

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Prescribing and Monitoring Clozapine Treatment

Appendix 9 – GP Referral Letter

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GP REFERRAL LETTER

Date / /

Dear Dr.....

Your patient is taking clozapine, an antipsychotic, which can be effective in patients who have failed to respond to, or are intolerant of, other neuroleptics.

The risk of agranulocytosis (about 0.7%) and neutropenia (about 3%) mean regular blood monitoring must be carried out for the duration of treatment with clozapine. White blood cell counts and absolute neutrophil counts are required weekly for the first 18 weeks of therapy (85% of cases occur during this period) and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of clozapine.

If infection occurs or blood tests indicate a significant drop in white cells, a repeat test should be carried out. A significant drop is a white blood cell count falling below $3.5 \times 10^9/L$ in the first 18 weeks of treatment or below $3.0 \times 10^9/L$ beyond week 18, or a single drop of $\leq 3 \times 10^9/L$ or a cumulative drop $\leq 3 \times 10^9/L$ within three weeks compared with the pre- clozapine baseline WBC.

Should this occur immediately consult.

The Clozaril(clozapine) Clinical Support Technician may also be contacted on 0800 838 909.

At each consultation a patient receiving clozapine should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints, such as fever or sore throat, and to other evidence of infection which may be indicative of neutropenia.

Each time the patient has a blood test done it is **important** to request that a copy be sent to both the dispensing pharmacy and Mylan New Zealand Limited. This ensures that the pharmacist can check the results before the medication is dispensed and blood results are also maintained on the Clozaril(clozapine) CarelinkPlus database. It is a condition of the supply of clozapine that all patients are registered on the Clozaril CareLinkPlus database.

Clozapine is a continuous therapy. If clozapine is not taken for more than **two days** for whatever reason, it is important to consult the data sheet section on "Re-starting therapy". The full clozapine data sheet can be downloaded at www.medsafe.govt.nz. If a single dose has been missed, and the patient's next dose is due within 4 hours, the missed dose is skipped and the next dose taken at the usual time. Otherwise, the missed dose should be taken as soon as the patient remembers, and then go back to taking it as they would do normally. The patient should not take a double dose to make up for the one that was missed.

It may be advantageous to counsel the patient about the importance of taking their medication regularly and the importance of regular blood monitoring. The next supply of clozapine can only be dispensed if the result from a recent blood test (<72 hours) is within the normal range.

The clozapine prescribing criteria has recently changed to allow general practitioners to continue the prescribing of clozapine for a specific patient whose illness is well-controlled in collaboration, or following consultation, with a Community Mental Health Team. Should you opt to write your patient's follow up prescriptions for clozapine, please ensure that patient's Consultant or Community Mental Health Team is consulted at all stages.

Should you have any queries please consult (Psychiatrist's name).

Yours sincerely,

Dr.....

Prescribing and Monitoring Clozapine Treatment

Appendix 10 - Clozapine Monograph

Clozapine Drug Monograph (abridged): *for complete reference refer to Medsafe datasheet*

Drug	Clozapine
Pharmacology	It has weak dopamine receptor-blocking activity at D1, D2, D3 and D5 receptors, but shows high potency for the D4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotonergic properties.
Pharmacokinetics	<p>The absorption of orally administered clozapine is 90% to 95%; neither the rate nor the extent of absorption is influenced by food.</p> <p>Clozapine is subject to first-pass metabolism, with a bioavailability of 50% to 60%. In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 L/kg.</p> <p>Clozapine is approximately 95% bound to plasma proteins. This means the terminal half-life is 12 hours (range: 6 to 26 hours).</p> <p>Clozapine is almost completely metabolised before excretion. Of the main metabolites only the desmethyl metabolite was found to be active.</p>
Indications	<p>Clozapine is indicated for patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.</p> <p>Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations.</p> <p>Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).</p>
Presentation	<ul style="list-style-type: none"> Tablets containing 25 mg and 100 mg clozapine. Clozapine 25mg tablets are light yellowish, round, flat with bevelled edges. It is scored with markings LO on one side, SANDOZ on the other side and 6.3mm in diameter. Clozapine 100mg tablets are light yellowish, round, flat with bevelled edges. It is scored with markings ZA on one side, SANDOZ on the other side and 10mm in diameter.
Route	Oral
Dose	<p>Starting therapy</p> <p>12.5 mg (half a 25-mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals.</p>

Prescribing and Monitoring Clozapine Treatment

Appendix 10 – Clozapine Monograph (continued)

Contraindications	<ul style="list-style-type: none"> • Known hypersensitivity to <i>clozapine</i> or to any of the excipients of Clozapine. • Patients unable to undergo regular blood tests. • History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy). • Impaired bone marrow function. • Uncontrolled epilepsy. • Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. • Circulatory collapse and/or CNS depression of any cause. • Severe renal or cardiac disorders (e.g. myocarditis). • Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure. • Paralytic ileus.
Precautions	<ul style="list-style-type: none"> • Previously adverse reaction to clozapine • Drugs known to depress bone marrow function should not be used concurrently with Clozapine. • Concomitant use of long-acting depot antipsychotics should be avoided. • Patients with a history of primary bone marrow disorders • Patients who have low WBC counts because of benign ethnic neutropenia
Adverse effects	<ul style="list-style-type: none"> • Blood and lymphatic system disorders • Common: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis • Uncommon : Agranulocytosis • Rare: Anaemia • Very rare: Thrombocytopenia, thrombocythaemia • Metabolism and nutrition disorders • Common: Weight gain • Rare : Impaired glucose tolerance, new onset diabetes, diabetes aggravated • Very rare: Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia • Psychiatric disorders • Common :Dysarthria • Uncommon: Dysphemia • Rare : Restlessness, agitation • Nervous system disorders • Very common: Drowsiness/sedation, dizziness • Common: Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks • Rare : Confusion, delirium • Very rare Tardive dyskinesia, obsessive compulsive symptoms • Cardiovascular disorders • Very common: Tachycardia • Common: ECG changes • Rare : Circulatory collapse, arrhythmias, myocarditis, pericarditis • Very rare: Cardiomyopathy • Vascular system disorders • Common: Hypertension, postural hypotension, syncope • Rare : Thromboembolism

Prescribing and Monitoring Clozapine Treatment

Appendix 11 - Clozapine Significant Side Effects and Management Advice

For full side effect list please refer to data sheet

1	Sedation	Re-adjust dose if persistent and/or re-adjust dose scheduling. Common in the early stages of dose titration.
2	Hypersalivation	This might respond to dose reduction. Alternative treatments may include anticholinergics (e.g. benztropine), clonidine or alpha-antagonists such as terazosin. Sub-lingual sprays of anti-cholinergics can be helpful, e.g. Ipratropium Inhaler.
3	Hyperthermia	Transient benign hyperthermia is not uncommon during the first three weeks of treatment with clozapine. It usually involves an increase of 0.5 - 1.5°C that spontaneously resolves over a few days with continued clozapine treatment. Temperature elevations above 38.5°C may require temporarily withholding of clozapine and further investigation for other causes.
4	Tachycardia	Common side effects that can affect a significant percentage of patients. Slow dose titration may reduce the risk of emergence of this side effect. It usually responds to dose reduction. If tachycardia persists, atenolol or metoprolol are usually effective in managing the tachycardia. ECG is required if tachycardia persists or is accompanied by raised CK level. Persistent tachycardia accompanied by high CK and eosinophilia might indicate the presence of myocarditis. In severe cases clozapine treatment must be discontinued.
5	Hypotension	Clozapine can lead to a postural drop in blood pressure.
6	Constipation	This is a common side effect which should be detected early and adequately treated. It usually responds to stool softeners, laxatives, fibre supplements and adequate fluid intake. Failure to treat constipation could result in serious complications such as toxic megacolon and aspirational pneumonia.
7	Haematological side effects	<ul style="list-style-type: none"> • Neutropenia 2.6%. • Leucocytosis can affect about 0.6% of patients. • Eosinophilia can affect up to 1% of patients. If eosinophil count is above $3.0 \times 10^9/L$ discontinue treatment. High eosinophil count specially if associated with tachycardia is a possible indication of an underlying myocarditis. • Agranulocytosis - affects about 0.8% of patients in the first year and declines in subsequent years. • Thrombocytopenia - Platelet count below $100 \times 10^9/L$ is associated with a high risk of bleeding. Clozapine should be discontinued if it drops below $50 \times 10^9/L$. • Lymphopenia - rare side effect. Discontinue if lymphocyte count is below $0.5 \times 10^9/L$.
8	Myocarditis and Cardiomyopathy	Rare but serious side effect. Myocarditis usually develops during the first few weeks of clozapine treatment, but cardiomyopathy may occur at any time. Warning symptoms include malaise, fatigue, chest pain, palpitations, dyspnoea and fever. Sometimes these symptoms are accompanied by peripheral eosinophilia. If a patient is suspected to have myocarditis, clozapine treatment must be terminated. An association between eosinophilia and myocarditis has been well documented however an association between myocarditis and clozapine induced eosinophilia has not been well established.
9	Myoclonic jerks	Responds to dose reductions. Sodium Valproate is effective in persistent cases and usually prevents progression to generalised seizures.

Prescribing and Monitoring Clozapine Treatment

Appendix 11 – Clozapine Significant Side Effects and Management Advice (continued)

10	Seizures	This is a dose related side effect which is more commonly associated with clozapine than with traditional antipsychotic medications, especially at doses over 450mg/day. This is another good reason for establishing the lowest possible dose of clozapine. Patients with pre-existing epilepsy can only be prescribed clozapine if their condition is stable.
11	Neuroleptic Malignant Syndrome (NMS)	This has been reported, though rarely, with clozapine treatment.
12	Hyperglycaemia	This is a rare side effect which has been reported in patients on clozapine treatment.
13	Weight Gain	Considerable weight gain can be a significant problem in some patients. Advice on diet and exercise should be given when the patient commences therapy.