


CHAPTER Health/Medical	CHAPTER 03	SECTION 001	SUBJECT 30
SECTION Drugs and Medication		DESCRIPTION Clozapine (Clozaril®)	
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APPLICATION:

<input checked="" type="checkbox"/> CMH Staff	<input type="checkbox"/> Board Members	<input checked="" type="checkbox"/> Provider Network	<input checked="" type="checkbox"/> Employment Services Providers
<input type="checkbox"/> Employment Services Provider Agencies	<input checked="" type="checkbox"/> Independent Contractors	<input type="checkbox"/> Students	<input checked="" type="checkbox"/> Interns
<input type="checkbox"/> Volunteers	<input checked="" type="checkbox"/> Persons Served		

POLICY:

Lapeer County Community Mental Health (LCCMH) prescribes and administers clozapine (Clozaril®) when indicated in accordance with the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program and Clozapine Tablets USP package insert.

STANDARDS:

- A. Clozapine (Clozaril®) is an atypical antipsychotic indicated for the treatment of severely ill patients with schizophrenia who fail to show an acceptable response or develop adverse effects to adequate courses of standard antipsychotic drug treatment.
- B. Clozapine is also indicated for reducing the risk of recurrent suicidal behavior in people with schizophrenia or schizoaffective disorder judged to be at chronic risk for re-experiencing suicidal behavior.

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- C. The requirements to prescribe, dispense, and receive clozapine are incorporated into a single, shared program called the Clozapine (REMS).
- D. The Clozapine REMS Program is used to manage the potential risk of severe neutropenia (absolute neutrophil count (ANC) less than 500/mm³) associated with clozapine treatment.
- E. The laboratory parameter used to monitor for clozapine-induced neutropenia is the Absolute Neutrophil Count (ANC) level, which is obtained from a complete blood count (CBC) with differential.
 - 1. ANC and CBC are monitored by an agency nurse and psychiatrist.
 - 2. Unusual lab values are reported immediately to the treating psychiatrist for appropriate clinical action.

PROCEDURES:

- A. Prior to Initiation of Treatment:
 - 1. Discuss contraindications including known serious hypersensitivity to clozapine or any other component of clozapine.
 - 2. Discuss the risk of severe neutropenia and appropriate monitoring requirements.
 - 3. Discuss risks involved including, but not limited, to orthostatic hypotension, bradycardia, syncope, seizure, myocarditis/cardiomyopathy, and increased mortality in the elderly with dementia-related psychosis.
 - 4. Advise to immediately report the appearance of signs/symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat).
 - 5. Obtain signed medication consent from the person served/guardian.

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6. Prescriber, designee, and pharmacy must become enrolled and certified online through the Clozapine REMS Program website or by submitting the enrollment forms via fax to the program contact center.
7. Prescriber (or designee) must enroll person served in the Clozapine REMS Program.
8. All stakeholders involved must comply with the Clozapine REMS Program requirements.
9. Prescriber (or designee) must obtain the ANC level and submit results to the Clozapine REMS Program prior to initiation of treatment and appropriately throughout treatment within 7 days prior to the delivery of the next supply of clozapine.

B. Initiation of Treatment:

1. Persons served in the general population with ANC $\geq 1500/\text{mm}^3$ are considered within normal range and are eligible to initiate treatment (refer to Exhibit 1 Table 1).
2. Persons served with Benign Ethnic Neutropenia (BEN) have ANC values lower than “standard” laboratory ranges for neutrophils and therefore require a different ANC monitoring algorithm for clozapine management. Consider hematology consultation before initiating or during clozapine treatment as necessary (refer to Exhibit 1 Table 1).
3. Prescriber follows the dosing information for initial titration in order to minimize the risk of hypotension, bradycardia, syncope, and cardiac arrest as these risks are highest during the initial titration period, particularly with rapid dose escalation. Initiate treatment at 12.5mg once or twice daily; titrate slowly; and use divided dosages (refer to Clozapine Tablets USP package insert 2.2).

C. Continuation of Treatment (refer to Exhibit 1 Table 1):

1. Regular ANC monitoring is required and based on the stage of therapy.

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- a. Weekly ANC monitoring is required during the first 6 months of treatment.
 - b. If ANC remains $\geq 1500/\text{mm}^3$ during the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months.
 - c. If the ANC remains $\geq 1500/\text{mm}^3$ for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.
2. Current ANC level must be reported in the Clozapine REMS Program and within the acceptable range or have an appropriate treatment rationale authorized by the prescriber.
 3. Generally, persons served responding to clozapine tablets should continue maintenance treatment on their effective dose beyond the acute episode.
- D. Increase monitoring Frequency (refer to Exhibit 1 Table 1):
1. Confirm all initial reports of ANC less than $1500/\text{mm}^3$ with a repeat ANC measurement within 24 hours.
 2. For mild neutropenia (1000 to $1499/\text{mm}^3$) continue treatment and monitor ANC three times weekly until $\geq 1500/\text{mm}^3$ and then return to prior monitoring frequency.
 3. For moderate neutropenia (500 to $999/\text{mm}^3$) interrupt treatment and monitor ANC daily until $\geq 1000/\text{mm}^3$, then 3 times weekly until $\geq 1500/\text{mm}^3$, then once weekly for 4 weeks, then return to prior monitoring frequency.
 4. For severe neutropenia (less than $500/\text{mm}^3$) interrupt treatment and monitor daily until ANC $\geq 1000/\text{mm}^3$, then monitor 3 times weekly until ANC $\geq 1500/\text{mm}^3$ and refer to a hematologist if physician deems necessary.
- E. Interruption of Treatment:
1. Suspected clozapine induced moderate neutropenia:

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- a. Recommend hematology consultation.
 - b. Re-initiate treatment once ANC normalizes to $\geq 1000/\text{mm}^3$ (refer to Exhibit 1 Table 1).
2. Suspected clozapine induced severe neutropenia:
- a. Recommend hematology consultation.
 - b. Do not resume treatment (referred to as rechallenged) unless prescriber documents a risk-benefit assessment determining that the benefits of treatment outweigh the risk of severe neutropenia (i.e. the 'treatment rationale').
 - c. Treatment may then be re-initiated under "Normal Range" monitoring once ANC $\geq 1500/\text{mm}^3$ (refer to Table 1).
3. Interrupt treatment as a precautionary measure if fever develops (101.3 F or greater) and obtain an ANC level (refer to Clozapine Tablets USP package insert 5.1).
- F. Re-initiation of Treatment:
1. Prescriber follows the re-initiation of treatment guidelines for titration to minimize the risk of hypotension, bradycardia, and syncope (refer to Clozapine Tablets USP package insert 2.5).
 - a. When restarting clozapine as a result of interruption (i.e., 2 days or more since the last dose), re initiate with 12.5 mg once daily or twice daily.
 - b. If well-tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment.
 2. ANC monitoring frequency is dependent on the level of neutropenia precipitating interruption and/or length of interruption (refer to Exhibit 1 Table 1).
- G. Discontinuation of Treatment:

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1. Method of treatment discontinuation will vary depending on the last ANC level.
 2. Prescriber follows the discontinuation of treatment guidelines (refer to Clozapine Tablets USP package insert 2.4).
 - a. If abrupt treatment discontinuation is necessary due to moderate to severe neutropenia, monitor ANC daily until $\geq 1000/\text{mm}^3$, then three times weekly until ANC $\geq 1500/\text{mm}^3$ (refer to Table 1).
 - b. For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of existing ANC monitoring is recommended for general population until ANC $\geq 1500/\text{mm}^3$.
 - c. In the event of planned termination of clozapine therapy with no evidence of moderate to severe neutropenia, reduce the dose gradually over a period of 1-2 weeks.
 3. Additional ANC monitoring is required with report of onset of fever (temperature of 101.3 F or greater) during the 2 weeks after discontinuation.
 4. Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to anticholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.
- F. Quality Assurance:
1. The Clozapine REMS Program is a strategy to manage known or potential risks associated with clozapine and is required by the Food and Drug Administration (FDA) to ensure that the benefits of clozapine outweigh the risk of severe neutropenia. All stakeholders involved in clozapine treatment are enrolled in this single, shared program and are required to comply with requirements.
 2. The Clozapine REMS Program uses an automated system that will alert the prescriber (or designee) if the ANC is overdue or if the ANC provided is below the recommended thresholds for mild, moderate, or severe neutropenia.

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3. The Clozapine REMS Program will change the treatment status of a patient with a low ANC to “interrupted” or “discontinued”, according to the recommendations in the Prescribing Information.
4. If the prescriber wishes to continue clozapine treatment, the prescriber (or designee) must change the treatment status to “active”, and the prescriber must confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (i.e. the ‘treatment rationale’).
5. Prior to dispensing clozapine, pharmacies must verify in the Clozapine REMS Program that the ANC is current (within 7 days of dispense date) and acceptable ($\geq 1000/\text{mm}^3$) or have a prescriber treatment rationale.

DEFINITION

Neutropenia – an abnormally low count of a type of white blood cells (neutrophils).

REFERENCES

Clozapine Tablets USP Package Insert
<https://www.clozapinerems.com>

EXHIBITS:

Table 1 – “Recommended Monitoring Frequency and Clinical Decisions by ANC Level”

SW:lr

This policy supersedes
#03.001.30 dated 09/23/2014.

CLOZAPINE REMS

Table 1

The Single Shared System for Clozapine No Blood, No Drug™

Recommended Monitoring Frequency and Clinical Decisions by ANC Level

ANC Level	Treatment Recommendation	ANC Monitoring
<p>Normal Range for a New Patient</p> <ul style="list-style-type: none"> General Population (ANC \geq 1500/μL) <p>BEN POPULATION</p> <ul style="list-style-type: none"> BEN Population (ANC \geq 1,000/μL) Obtain at least two baseline ANC levels before initiating treatment 	<ul style="list-style-type: none"> Initiate treatment If treatment interrupted: <ul style="list-style-type: none"> < 30 days, continue monitoring as before \geq 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia 	<ul style="list-style-type: none"> Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months See Section 2.4 of the full Prescribing Information
<p>Mild Neutropenia (1000 to 1499/μL)*</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Continue treatment <p>BEN POPULATION</p> <ul style="list-style-type: none"> Mild Neutropenia is normal range for BEN population, continue treatment Obtain at least two baseline ANC levels before initiating treatment If treatment interrupted <ul style="list-style-type: none"> < 30 days, continue monitoring as before \geq 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia 	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Three times weekly until ANC \geq 1500/μL Once ANC \geq 1500/μL, return to patient's last "Normal Range" ANC monitoring interval** <p>BEN POPULATION</p> <ul style="list-style-type: none"> Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months See Section 2.4 of the full Prescribing Information
<p>Moderate Neutropenia (500 to 999/μL)*</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Resume treatment once ANC normalizes to \geq 1000/μL <p>BEN POPULATION</p> <ul style="list-style-type: none"> Recommend hematology consultation Continue treatment 	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Daily until ANC \geq 1000/μL, then Three times weekly until ANC \geq 1500/μL Once ANC \geq 1500/μL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval** <p>BEN POPULATION</p> <ul style="list-style-type: none"> Three times weekly until ANC \geq 1000/μL or \geq patient's known baseline. Once ANC \geq 1000/μL or patient's known baseline, then check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**
<p>Severe Neutropenia (less than 500/μL)*</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks <p>BEN POPULATION</p> <ul style="list-style-type: none"> Recommend hematology consultation Interrupt treatment for suspected clozapine induced neutropenia Do not rechallenge unless prescriber determines benefits outweigh risks 	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Daily until ANC \geq 1000/μL Three times weekly until ANC \geq 1500/μL If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC \geq 1500/μL <p>BEN POPULATION</p> <ul style="list-style-type: none"> Daily until ANC \geq 500/μL Three times weekly until ANC \geq patients established baseline If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC \geq 1000/μL or at patient's baseline

* Confirm all initial reports of ANC less than 1500/ μ L (ANC < 1000/ μ L for BEN patients) with a repeat ANC measurement within 24 hours

** If clinically appropriate