LAPEER COUNTY COMMUNITY MENTAL HEALTH **Date Issued** 04/13/2016
Date Revised

CHAPTER Health/Medical	**CHAPTER** 03	**SECTION** 001	**SUBJECT** 30
SECTION Drugs and Medication	**DESCRIPTION** Clozapine (Clozaril®)		
WRITTEN BY Jennifer Rayburn RN, BSN	**REVISED BY**	**AUTHORIZED BY** Robert M Sprague, CEO 5/2/16 Dr. Robert M. Sprague, CEO	

APPLICATION:

► CMH Staff ► CMH Provider Network

POLICY:

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. 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. The requirements to prescribe, dispense, and receive clozapine are incorporated into a single, shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS). 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. The laboratory parameter used to monitor for clozapine-induced neutropenia is the ANC level which is obtained from a complete blood count (CBC) with differential. Standards stated in this policy are in accordance with the Clozapine REMS Program and the Clozapine Tablets USP package insert.

STANDARDS:

Prior to Initiation of Treatment:

A. Discuss contraindications including known serious hypersensitivity to clozapine or any other component of clozapine.
B. Discuss the risk of severe neutropenia and appropriate monitoring requirements.

C. 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.
D. Advise to immediately report the appearance of signs/symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat).
E. Obtain signed medication consent from the person served/guardian.
F. 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.
G. Prescriber (or designee) must enroll person served in the Clozapine REMS Program.
H. All stakeholders involved must comply with the Clozapine REMS Program requirements.
I. 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.

Initiation of Treatment:

A. Persons served in the general population with ANC >= 1500/mm3 are considered within normal range and are eligible to initiate treatment (refer to Table 1).
B. Persons served with Benign Ethnic Neutropenia (BEN) have ANC values that are 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 Table 1).
C. 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).

Continuation of Treatment (refer to Table 1):

A. Regular ANC monitoring is required and based on the stage of therapy.
    1. Weekly ANC monitoring is required during the first 6 months of treatment.

2. If ANC remains >= 1500/mm3 during the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months.
3. If the ANC remains >= 1500/mm3 for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

B. 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.
C. Generally, persons served responding to clozapine tablets should continue maintenance treatment on their effective dose beyond the acute episode.

Increase monitoring Frequency (refer to Table 1):

A. Confirm all initial reports of ANC less than 1500/mm3 with a repeat ANC measurement within 24 hours.
B. For mild neutropenia (1000 to 1499/mm3) continue treatment and monitor ANC three times weekly until >=1500/mm3 and then return to prior monitoring frequency.
C. For moderate neutropenia (500 to 999/mm3) interrupt treatment and monitor ANC daily until >= 1000/mm3, then 3 times weekly until >=1500/mm3, then once weekly for 4 weeks, then return to prior monitoring frequency.
D. For severe neutropenia (less than 500/mm3) interrupt treatment and monitor daily until ANC >= 1000/mm3, then monitor 3 times weekly until ANC >= 1500/mm3.

Interruption of Treatment:

A. Suspected clozapine induced moderate neutropenia:
    1. Recommend hematology consultation.
    2. Re-initiate treatment once ANC normalizes to >= 1000/mm3 (refer to Table 1).
B. Suspected clozapine induced severe neutropenia:
    1. Recommend hematology consultation.
    2. 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').

3. Treatment may then be re-initiated under "Normal Range" monitoring once ANC >=1500/mm3 (refer to Table 1).

C. 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).

Re-initiation of Treatment:

A. 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).
   1. 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.
   2. If well-tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment.
B. ANC monitoring frequency is dependent on the level of neutropenia precipitating interruption and/or length of interruption (refer to Table 1).

Discontinuation of Treatment:

A. Method of treatment discontinuation will vary depending on the last ANC level.
B. Prescriber follows the discontinuation of treatment guidelines (refer to Clozapine Tablets USP package insert 2.4).
   1. If abrupt treatment discontinuation is necessary due to moderate to severe neutropenia, monitor ANC daily until >=1000/mm3, then three times weekly until ANC >=1500/mm3 (refer to Table 1).
   2. For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of existing ANC monitoring is recommended for general population until ANC >=1500/mm3.
   3. 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.
C. Additional ANC monitoring is required with report of onset of fever (temperature of 101.3 F or greater) during the 2 weeks after discontinuation.

D. 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.

Quality Assurance:

A. 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.
B. 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.
C. 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.
D. 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').
E. 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 (>=1000/mm3) or have a prescriber treatment rationale.

REFERENCES

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

EXHIBITS:

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

JR:mgr

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

Table 1

CLOZAPINE REMS

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
Normal Range for a New Patient • General Population (ANC ≥ 1500/μL)	• Initiate treatment • If treatment interrupted: - < 30 days, continue monitoring as before - ≥ 30 days, monitor as if new patient	• Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
BEN POPULATION • BEN Population (ANC ≥ 1,000/μL) • Obtain at least two baseline ANC levels before initiating treatment	• Discontinuation for reasons other than neutropenia	• See Section 2.4 of the full Prescribing Information
Mild Neutropenia (1000 to 1499/μL)*	**GENERAL POPULATION** • Continue treatment	**GENERAL POPULATION** • Three times weekly until ANC ≥ 1500/μL • Once ANC ≥ 1500/μL, return to patient's last "Normal Range" ANC monitoring interval**
	BEN POPULATION • Mild Neutropenia is normal range for BEN population, continue treatment • Obtain at least two baseline ANC levels before initiating treatment • If treatment interrupted - < 30 days, continue monitoring as before - ≥ 30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	**BEN POPULATION** • 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
Moderate Neutropenia (500 to 999/μL)*	**GENERAL POPULATION** • Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Resume treatment once ANC normalizes to ≥ 1000/μL	**GENERAL POPULATION** • Daily until ANC ≥ 1000/μL, then • Three times weekly until ANC ≥ 1500/μL • Once ANC ≥ 1500/μL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**
	BEN POPULATION • Recommend hematology consultation • Continue treatment	**BEN POPULATION** • Three times weekly until ANC ≥ 1000/μL or ≥ patient's known baseline. • Once ANC ≥ 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**
Severe Neutropenia (less than 500/μL)*	**GENERAL POPULATION** • Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	**GENERAL POPULATION** • Daily until ANC ≥ 1000/μL • Three times weekly until ANC ≥ 1500/μL • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/μL
	BEN POPULATION • Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	**BEN POPULATION** • Daily until ANC ≥ 500/μL • Three times weekly until ANC ≥ patients established baseline • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/μL or at patient's baseline

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

** If clinically appropriate

Source: *Clozapine and the Risk of Neutropenia: An Overview for Healthcare Providers*

Version 2.0 – December 23, 2014