



**PRISONS**  
**Health and Wellness Services**  
**Policies and Procedures**

<b>Title</b>	<b>Use of Clozapine</b>			
<b>Section</b>	TX II-25	<b>Issue Date</b> December 3, 2020	<b>Supersedes Date</b> June 2016	<b>Next Review Date</b> December 2021

**References**

**Performance-Based Standards and Expected Practices for Adult Correctional Institutions, 5<sup>th</sup> Edition 5-ACI-6A-18 (M), 5-ACI-6C-04 (M); NC DHHS, Division of State Operated Healthcare Facilities**

**I. PURPOSE**

To establish policy and procedures for the use of clozapine in NCDPS facilities

**II. POLICY**

Clozapine is a Food and Drug Administration (FDA) approved drug for treatment resistant schizophrenia and for the reduction in risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorders. In addition, clinically it may offer hope of improvement for treatment of other conditions that have not responded to other psychotropic medications.

**III. DEFINITIONS**

- (a) Absolute Neutrophil Count (ANC): WBC X% neutrophils.
- (b) Benign ethnic neutropenia (BEN): condition in certain ethnic groups whose average ANCs are lower than standard.
- (c) Complete blood count (CBC) with differential: blood test that provides the absolute neutrophil count and panic values that conform to the clozapine guidelines.
- (d) Designee: A health care provider other than the prescriber who can enroll patients, enter ANC values on the prescriber's behalf, and review patient lists and patient lab history, designated by the prescriber.
- (e) General Population (GP): for purposes of this policy and clozapine monitoring, the general population are all patients without BEN.



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- (f) Risk Evaluation and Mitigation Strategy (REMS): strategy to manage known or potential risks associated with a drug or group of drugs. REMS are required for clozapine to ensure the potential benefits outweigh the risk of neutropenia.

**IV. PROCEDURE**

- (a) Criteria for Consideration in Initiating Treatment

- (1) Prior to the initiation of clozapine, consideration of the following should be made by the attending physician:

- (A) Diagnoses- DSM 5 diagnosis of schizophrenia, schizoaffective disorder, refractory bipolar disorder, or borderline personality disorder. Clozapine may be indicated for use in other disorders where there are treatment resistant, signs/symptoms of mental illness.

- (B) Severity of Illness/Side Effects Characterized by:

- (i) Prominent positive and/or negative symptoms, conceptual disorganization, violent behavior directed at others, or suicidal/self-injurious thoughts or behavior.
- (ii) Lack of responsiveness to other antipsychotic medication at an adequate dose and for an adequate duration. Typically, two (2) antipsychotics have been tried.
- (iii) Tardive Dyskinesia - Persistent tardive dyskinesia with disabling psychotic symptoms while not taking antipsychotic medication.
- (iv) Extrapyrimal Side Effects - Severe, drug-induced, extrapyramidal side effects which cannot be managed with either anti-Parkinsonian drugs or by reducing the dose of the antipsychotic medication.

- (C) Opportunity for improved quality of life - Considerations should include a reasonable expectation of the patient living more independently in the



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facility or an improved quality of life while in the hospital.

- (D) Clozapine initiations should preferably occur at the 2 inpatient facilities, CP or NCCIW. However, any M-3 offender is potentially eligible to receive clozapine and requests for exceptions should be directed to the Chief of Psychiatry or designee before initiating. All M-3 facilities or M-4 facilities will accept patients already initiated on Clozapine.

(b) Clinical Guidelines

(1) Registration

- (A) Physicians must be registered with the Clozapine REMS Program before prescribing clozapine.
- (B) Physicians must approve a pharmacy designee to enroll patients and enter ANC results on the prescriber's behalf in the Clozapine REMS program.

(2) Education/Informed Consent

- (A) Prescribers shall provide the offender with information about Clozapine.
- (B) Prescribers must inform the offender about the risk of severe neutropenia associated with clozapine.
- (C) Informed consent should be obtained from the offender prior to the initiation of clozapine therapy and documented on the *Clozapine Informed Consent form*. (Attachment 1). Completed informed consent document will be scanned into the patient's health care record.
- (D) The patient should be willing and able to cooperate in taking oral medications and allowing required blood testing.

(3) Patients admitted to facilities and already actively taking clozapine



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- (A) Complete steps (2) (A) and (B) under "Clinical Guidelines."
  - (B) Complete step (F) "Prescribing."
  - (C) Upon receipt of a CBC with differential completed within the last seven days, or as compliant with the REMS schedule, clozapine can be dispensed for the patient if the ANC is at least 1500 for the GP or at least 1000 for patients with BEN. Blood work from an outside agency is acceptable if within the last 7 days or as compliant with the REMS schedule.
- (4) Prescribing
- (A) DOP Health and Wellness Central Office will establish a Clozapine Committee consisting of the Chief of Psychiatry, Pharmacists, UNC Psychiatrist with expertise in Clozapine. This committee will be available to consult on whether an offender is appropriate for Clozapine and for questions about titration, side effects, or logistic concerns.
  - (B) Required pre-Clozapine baseline studies include a CBC with differential, a myocarditis panel (Troponin-I, CRP, BNP) and ECG.
  - (C) The Committee may impose additional requirements which must be met prior to the initiation of Clozapine.
  - (D) Patients must be enrolled in the Clozapine REMS Program before Clozapine can be dispensed and/or administered. A patient can be enrolled one of two ways: by logging into the website and enrolling or completing the "Patient Enrollment form" and faxing the form into the program.
  - (E) Attending psychiatric physicians are responsible for initial and subsequent dosing decisions based on clozapine prescribing information published by the manufacturer.



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- (F) Prior to initiation of clozapine, the patient must have a current (no older than seven (7) days) ANC that meets the minimum standards recommended by the Clozapine REMS Program. If a Clozapine patient has had an interruption in Clozapine treatment of greater than 48 hours, restart with 12.5 mg once or twice daily to minimize the risk of hypotension, bradycardia and syncope. There are clinical circumstances whereby starting at a higher dose could be justified. Following the consultant's review, the rationale for starting at the higher dose should be documented in the patient's healthcare record.
  
- (G) Consideration should be given in some cases to ordering that the medication be given as crushed and floated. This would be based on the prescriber's assessment of the patients anticipated medication compliance. Factors to be considered include:
  - (i) Patients clinical state in which they may be very psychotic and ambivalent about taking any medication,

or

  - (ii) Patients that are very depressed and might consider hoarding medications to possibly self-injure by over dosing;

or

  - (iii) There is a potential for misuse due to a desire for a secondary gain (examples include hoarding medications in order to sell them or to take a large quantity at once in order to get "high".

(c) **Monitoring**

- (1) The attending psychiatrist orders a weekly CBC with differential (or less frequently as described below). The pharmacist or designee checks the ANC information for each patient with labs scheduled for that day. Each patient's ANC is reported to the Clozapine REMS Program. Missing results are investigated by



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the pharmacist to determine the reason for omission. If the CBC was not drawn on the designated day, nurse supervisor on the unit (and, if necessary, the prescriber) are verbally contacted to request a CBC within 24 hours. If a patient's ANC is less than 1500 then the Laboratory notifies the attending psychiatric physician and Pharmacy. Additional laboratory monitoring or termination of Clozapine may be necessary as recommended by the Clozapine REMS Program guidelines.

- (2) Patients first started on Clozapine have an ANC monitored weekly for the first 6 months. If ANC has remained acceptable for this six-month period, then the frequency of monitoring ANC may be decreased to every 2 weeks for the next 6 months. If ANC remains acceptable during this next 6-month period, the monitoring frequency may be decreased to every 4 weeks.
- (3) Metabolic monitoring should be done for all patients on anti-psychotic medications in accordance with recommended guidelines.
- (4) The attending psychiatrist, in consultation with the medical physician, reviews baseline Clozapine laboratory results and initiates the *Myocarditis Symptom Progress Note for Patients on Clozapine* (Attachment 2) at the end of the first week of treatment and for an additional 4 weeks. The designated physician will review weekly myocarditis monitoring labs and bring significant abnormalities promptly to the attention of the attending psychiatrist. The form, if used will be scanned into the patient's healthcare record, only if the clinical information is not otherwise mentioned in the healthcare record.
- (5) In order to monitor for the development of Clozapine related Myocarditis, a Myocarditis Panel (Troponin, CRP and BNP) and EKG are performed prior to initiation of Clozapine then for 4 weeks. An EKG is performed prior to initiation of Clozapine as a baseline and not repeated routinely unless indicated. This will be written by the attending psychiatrist as a recurring laboratory order in patient's healthcare record.
- (6) Recommended actions to be taken when the monitoring for signs and symptoms or tests raise a concern for Clozapine related Myocarditis are summarized in



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tables below.

Table 1: Recommended Monitoring for the Signs of Myocarditis

<b>Clinical</b>	<b>Actions</b>
Signs of Infectious illness or Myocarditis	Daily evaluation, daily Myocarditis Panel & Vital Signs at least twice a day (BID). EKG frequency using clinical judgment
HR 2: 120 bpm	
CRP 50-100	
Troponin > 2X upper limits normal	
Significant increase in BNP from baseline	Assess whether rise could be due to Clozapine or other medical condition
EKG Changes	Assess whether EKG changes may be related to Clozapine

Table 2: Recommendations for Monitoring Myocarditis After Discontinuation of Clozapine

<b>Clinical</b>	<b>Actions</b>
Acute Myocarditis identified or strongly suspected	Stop Clozapine, Cardiology consult, if clinically indicated
Troponin > 2 X upper limits normal	
CRP > 100	

(d) Dispensing

- (1) Clozapine will be obtained directly from the pharmacy subsequent to the psychiatrist writing patient - specific orders based on the laboratory monitoring



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parameters.

- (2) Nursing can obtain Clozapine as long as blood level values are within acceptable limits.
- (3) If a CBC with differential is not obtained, the Clozapine is **NOT** immediately stopped. The charge nurse on the patient care unit is notified and informed of the need for the lab work. If the lab work is not received within 2 days, the prescribing psychiatric physician is contacted and informed Clozapine will be discontinued unless the CBC with differential is obtained.
- (4) Treatment Recommendations
  - (i) Follow guidelines in Attachment 3: *Recommended Monitoring Frequency and Clinical Decisions by ANC level. (Rems Recommendations)*
- (e) Notification of Others
  - (A) The Pharmacy notifies the prescribing psychiatric physician if Clozapine must be discontinued.
- (f) Discontinuation
  - (1) The attending psychiatrist is responsible for discontinuing Clozapine based on the patient/guardian's request, lack of therapeutic response, side effects or unacceptable ANC results. The attending physician schedules ANC monitoring following Clozapine REMS Program guidelines.
  - (2) If Clozapine is discontinued for neutropenia, follow guidelines in Table 2: *Recommendations for Monitoring Myocarditis After Discontinuation of Clozapine.*
- (g) Prescription of Clozapine at Discharge
  - (1) The patient's treatment team provides the patient's outpatient provider the date of





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the last CBC with differential and the current monitoring frequency.

- (2) A seven-day continuation supply of Clozapine is offered to all patients transferring to another facility or releasing from prison. The patient may receive up to a 28-day supply, if permitted, based on the appropriate ANC monitoring frequency per the Clozapine REMS requirements and documentation in the Clozapine registry.

**V. Any exceptions to the above policy must be approved by the Chief of Psychiatry/designee.**

\_\_\_\_\_  
 Todd E. Ishee  
 Commissioner of Prisons

12/03/20  
 Date

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

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

\*\* If clinically appropriate

**North Carolina Department of Safety  
Division of Prisons Health and Wellness**

**CLOZAPINE INFORMED CONSENT**

Patient's Name: \_\_\_\_\_

OPUS #: \_\_\_\_\_

I understand that Clozapine is presently approved for or has been shown to help psychiatric conditions such as mine and that my Doctor has recommended it for me.

I understand that this medicine can have side effects like rapid heartbeat, higher body temperature, increased salivation, drowsiness, dizziness, constipation, weight gain, and high levels of fat or sugar in the blood.

Clozapine can have rare, but serious side effects like seizures, pulmonary emboli, or an inflammation of the heart that may cause death. Blood will be drawn regularly to check for heart inflammation.

A condition called severe neutropenia (decrease of a type of white blood cells) can occur in about one out of 100 patients taking clozapine. With proper monitoring, this can be detected quickly and Clozapine will be stopped. For this reason, I agree to get my blood tested every week for at least six (6) months, then every other week for another six months, then once a month for as long as I stay on this medication. If I refuse blood tests the Pharmacist cannot give me the clozapine. If I stop taking Clozapine, I will be required to get my blood tested as directed by my doctor.

I agree to tell my doctor immediately if I do not feel well, as this could be an early sign of a problem with Clozapine.

I agree to release information about my blood counts to the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. This is to assure that Clozapine can be used safely.

I have discussed other treatments for my illness as well as risks and benefits of taking Clozapine with my Doctor.

I have read and understand this consent form and give my permission voluntarily for Clozapine treatment.

\_\_\_\_\_  
Patient's/Guardian's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Physician's Signature

\_\_\_\_\_  
Date

**MYOCARDITIS SYMPTOM PROGRESS NOTE FOR PATIENTS ON CLOZAPINE**

To be Completed Weekly for 4 weeks

Date of Clozapine Initiation: \_\_\_ / \_\_\_ / \_\_\_ -

Does the patient have any of the following symptoms?

CIRCLE WEEK#      2   3   4

1. Fatigue or decreased exercise capacity?

\_\_\_ No \_\_\_ Yes, explain:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

2. Dyspnea. orthopnea?

\_\_\_ No \_\_\_ Yes, explain:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

3. Complaints of Chest Pain, Pressure?

\_\_\_ No \_\_\_ Yes, explain:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

4. Persistent Palpitations?

\_\_\_ No \_\_\_ Yes, explain:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

5. Fever or Flu-like symptoms?

\_\_\_ No \_\_\_ Yes, explain:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

6. Peripheral Edema?

\_\_\_ No \_\_\_ Yes, explain:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

7. If the answer to any of the questions above is yes. please order CBC with differential, Myocarditis panel and KKG.

Physician's Printed Name and Signature: \_\_\_\_\_

Date: \_\_\_\_\_