

CLOZAPINE REMS

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

This guide is intended to educate Healthcare Providers about clozapine and the Clozapine REMS Program. During the launch of the Clozapine REMS Program, there were challenges that required an extension of the phased implementation period. This guide is reflective of the full implementation of the Clozapine REMS Program, which is expected in [TBD]. For the current state of the Clozapine REMS Program, expected full implementation dates and important updates on the transition period, please see the *Clozapine REMS Frequently Asked Questions (FAQs)* on the Clozapine REMS Program Website at www.clozapinerems.com.

Clozapine and the Risk of Neutropenia:

A Guide for Healthcare Providers

This Guide discusses:

- What is the Clozapine REMS Program?
- Clozapine and the risk of severe neutropenia
- Treatment recommendations and patient absolute neutrophil count (ANC) monitoring
- Prescriber requirements for the Clozapine REMS Program
- Pharmacy requirements for the Clozapine REMS Program

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1 The Clozapine REMS Program

Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/ μ L). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs, and is required by the Food and Drug Administration (FDA) for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia.

The Clozapine REMS Program provides a **centralized** point of access:

1. For **prescribers** and **pharmacies** to certify before prescribing or dispensing clozapine
2. To enroll and manage **patients** on clozapine treatment

Clozapine is available by prescription as:

- Clozaril® (clozapine) tablets, for oral use
- Versacloz® (clozapine, USP) oral suspension
- Clozapine, USP, orally disintegrating tablets
- Approved generic equivalents of these products

To minimize the risk of severe neutropenia associated with the use of clozapine, the Clozapine REMS Program includes the following key program requirements:

Prescribers (who prescribe clozapine for outpatient use)

- Must certify in the Clozapine REMS Program to prescribe clozapine
- Must enroll all patients in the Clozapine REMS Program
- Must submit patients' ANCs to the Clozapine REMS Program for every prescription of clozapine according to the patient's monitoring frequency:
 - For weekly monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 7 days of the lab draw* date
 - For every two weeks monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 15 days of the lab draw* date
 - For monthly monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 31 days of lab draw* date

*Assumes the lab draw date is day 0

Pharmacies

- Must certify in the Clozapine REMS Program to dispense clozapine
- Must verify the prescriber is certified and the patient is enrolled prior to dispensing clozapine
- Must verify the ANC is within the acceptable range described in the Prescribing Information, or that the prescriber has authorized the continuation of clozapine treatment by providing a "Treatment Rationale" for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits outweigh the risks of developing severe neutropenia
- Prior to dispensing clozapine, verify ANC is current (within 7/15/31 days prior to the "Predispense Authorization"/"Eligibility Check" transaction date)

Patients

- Must be enrolled in the Clozapine REMS Program by a certified prescriber to receive clozapine
- Must comply with the ANC testing requirements

Important Terms Used in the Clozapine REMS Program:

- **Predispose Authorization (PDA):** An authorization given to outpatient pharmacies which reflects that the safe-use conditions for that patient have been met. The PDA is an electronic code provided by the Clozapine REMS Program verifying that the patient is enrolled, the prescriber and pharmacy are certified, and that the ANC is on file, current and within acceptable range. This PDA then permits dispensing of clozapine to the patient.
- **Treatment Rationale (TR):** A justification used by a prescriber to allow a patient having moderate neutropenia (ANC 500-999/ μ L for the general population) or severe neutropenia (ANC < 500/ μ L for general population and patients with documented BEN) to continue treatment. Only prescribers can confirm that benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia.
- **Dispense Rationale (DR):** The opportunity provided by the Clozapine REMS Program to certified outpatient pharmacies to apply clinical judgment and continue to dispense clozapine to enrolled patients when a patient's prescriber is not certified in the Clozapine REMS Program. The Clozapine REMS Program alerts the pharmacy if the prescriber is not certified in the Clozapine REMS Program, and prevents a PDA from being issued for a clozapine dispense unless the pharmacy provides a "Dispense Rationale" authorizing dispensing. The *Dispense Rationale* is valid for only 72 hours (3 calendar days) and can be provided a maximum of 3 times in a rolling six-month period.
- **Eligibility Check (EC):** The process inpatient pharmacies use to determine whether a patient can receive clozapine. Obtained by using the Clozapine REMS Program Website or Clozapine REMS Program Call Center, the EC verifies the patient is enrolled, the ANC is on file, current, and within acceptable range.
- **Inpatient pharmacy:** a pharmacy within a facility dispensing clozapine only to patients receiving inpatient medical care and other related services for surgery, acute medical conditions or injuries (usually for a short-term illness or condition).
- **Outpatient pharmacy:** a pharmacy dispensing clozapine only to patients treated on an outpatient or chronic basis. This includes, but is not limited to, retail drug-stores, ambulatory care pharmacies, and pharmacies dispensing to long-term care, rehabilitation facilities and prison systems.
- **Absolute neutrophil count (ANC):** laboratory parameter for monitoring patients for clozapine-induced neutropenia.
- **Benign Ethnic Neutropenia (BEN):** a condition observed in certain ethnic groups whose average ANC is lower than "standard" laboratory ranges for neutrophils compared to the general population. Patients with documented BEN have a separate ANC monitoring algorithm when treated with clozapine.

2 Absolute Neutrophil Count (ANC), Neutropenia, and Patient ANC Monitoring

What is ANC?

Absolute neutrophil count (ANC) is the laboratory parameter for monitoring patients for clozapine-induced neutropenia. Prescribers must submit the ANC before starting and during clozapine treatment.

ANC is usually available as a component of the complete blood count (CBC), including differential:

- ANC is more relevant to drug-induced neutropenia than white blood cell (WBC) count
- ANC may also be calculated using the following formula:

$$\text{Absolute Neutrophil Count} = \text{Total WBC Count} \times \text{Total percentage of neutrophils* obtained from the differential}$$

*neutrophils include “segs” and “bands”

Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary.

What is the risk of severe neutropenia associated with clozapine?

Clozapine can cause severe neutropenia, which can lead to serious infections and death. Severe neutropenia occurs in a small percentage of patients taking clozapine.

- Severe neutropenia is defined as ANC less than 500/ μ L
- Severe neutropenia replaces the previous terms “severe leukopenia,” “severe granulocytopenia,” and “agranulocytosis”
- The risk appears greatest during the first 18 weeks of clozapine treatment
- The mechanism is not dose-dependent
- It is unclear if concurrent use of other drugs known to cause neutropenia increases the risk or severity of clozapine-induced neutropenia
- If clozapine is used concurrently with a medication(s) known to cause neutropenia:
 - Consider monitoring patients more closely than the treatment guidelines recommend, and
 - Consult with the treating oncologist in patients receiving concomitant chemotherapy

For a complete discussion of other risks, including other Boxed Warnings, please see the Prescribing Information available at www.clozapinerems.com.

What is Benign Ethnic Neutropenia (BEN)?

BEN is a condition observed in certain ethnic groups whose average ANC's are lower than "standard" laboratory ranges for neutrophils. Because of this condition, patients who have documented BEN have a separate ANC monitoring algorithm when treated with clozapine.

When enrolling a patient in the Clozapine REMS Program, identify if the patient has documented BEN, so the patient is monitored according to the correct ANC monitoring algorithm.

A few important things to know about patients with documented BEN:

- It is most commonly observed in individuals of African descent (approximate prevalence of 25-50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin
- BEN is more common in men
- Patients with BEN have normal hematopoietic stem cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections
- Patients with BEN **are not** at increased risk for developing clozapine-induced neutropenia

Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider a hematology consultation before starting or during clozapine treatment as necessary.

What are the treatment recommendations and monitoring requirements for patients taking clozapine?

The recommended ANC monitoring frequency for patients in the general population as well as patients who have documented BEN is shown in [Table 1](#). The table also provides recommendations for monitoring patients who experience a decrease in ANC during the course of treatment.

Patients may transition to less frequent ANC monitoring based on the number of weeks of continuous clozapine therapy and the patient's ANC's. Weekly ANC monitoring is required for all patients during the first six months of treatment. If the ANC remains in the normal range (ANC greater than or equal to 1500/ μ L for the general population, ANC greater than or equal to 1000/ μ L for patients with BEN) for the first six months of therapy, monitoring frequency can be reduced to every two weeks. If the patient's ANC continues to remain in the normal range for the second six months of treatment, ANC monitoring may be reduced to monthly.

The Clozapine REMS Program will alert prescribers via their website dashboard when a patient qualifies for a change in ANC monitoring frequency.



Before starting treatment with clozapine, the baseline ANC must be:

- at least 1500/ μ L for the general population
- at least 1000/ μ L for patients with documented BEN

During treatment, monitor ANC regularly as described in [Table 1](#) below.

Table 1 Recommended Monitoring Frequency and Clinical Decisions by ANC Level

ANC Level	Treatment Recommendation	ANC Monitoring
Normal Range for a New Patient GENERAL POPULATION • ANC \geq 1500/ μ L BEN POPULATION • ANC \geq 1000/ μ L • 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 six months • Every two weeks from 6 to 12 months • Monthly after 12 months • See Section 2.4 of the Prescribing Information
Mild Neutropenia (1000 - 1499/ μ L)*	GENERAL POPULATION <ul style="list-style-type: none"> • Continue treatment BEN POPULATION <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 	GENERAL POPULATION <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** BEN POPULATION <ul style="list-style-type: none"> • Weekly from initiation to six months • Every two weeks from 6 to 12 months • Monthly after 12 months • See Section 2.4 of the Prescribing Information
Moderate Neutropenia (500 - 999/ μ L)*	GENERAL POPULATION <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 BEN POPULATION <ul style="list-style-type: none"> • Recommend hematology consultation • Continue treatment 	GENERAL POPULATION <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** BEN POPULATION <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, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**
Severe Neutropenia (< 500/ μ L)*	GENERAL POPULATION <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 BEN POPULATION <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 	GENERAL POPULATION <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 BEN POPULATION <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

Can a patient continue clozapine treatment with an ANC less than 1000/ μ L?

For Patients in the General Population

Yes; prescribers may choose to continue clozapine treatment in patients with ANCs less than 1000/ μ L. However, prescribers should follow the treatment recommendations as noted in [Table 1](#) and carefully determine if the benefits of continuing clozapine treatment outweigh the risks.

The recommendations to interrupt treatment are provided to ensure patient safety. If monitoring ANC and symptoms of infection is not done appropriately, patients with ANCs less than 1000/ μ L are at risk for developing complications of severe neutropenia including serious infection and death.

Refer to [Section 3](#) of this document for more details on how to authorize a patient to continue treatment.

For Patients with documented BEN

Yes; the Prescribing Information for clozapine recommends interrupting clozapine treatment for patients with BEN only when the ANC is less than 500/ μ L. No interruption in treatment is recommended for ANC 500-999/ μ L, although a hematology consultation is recommended.

If a patient develops a fever, how is clozapine treatment managed?

Generally, clozapine treatment should be interrupted as a precautionary measure in any patient who develops a fever of 38.5°C (101.3°F) or greater, and an ANC should be obtained. Fever is often the first sign of a neutropenic infection.

If fever occurs in any patient with an ANC less than 1000/ μ L, initiate appropriate neutropenia work-up and treatment for infection. Refer to [Table 1](#) for ANC monitoring recommendations.

If any patient presents with evidence of fever and/or neutropenia, consider a hematology consultation.

How is clozapine discontinued for neutropenia?

The method of treatment discontinuation will vary depending on the patient's most recent ANC result. Abrupt treatment discontinuation is necessary for moderate to severe neutropenia that you suspect is caused by clozapine.



REMEMBER to submit the decision to discontinue clozapine for a patient to the Clozapine REMS Program. You can complete it one of three ways:



By signing in to the Clozapine REMS Program Website at www.clozapinerems.com



By calling the Clozapine REMS Program Contact Center at 844-267-8678



By completing the “Patient Update – Change Treatment Status” section of the *Clozapine REMS ANC Lab Reporting Form* and faxing it to the Clozapine REMS Program at 844-404-8876

How is a patient monitored if clozapine treatment is discontinued for neutropenia?

After **discontinuing** clozapine, monitor ANC according to the recommendations in [Table 2](#) as shown below.

Table 2: Recommended monitoring frequency when clozapine treatment is discontinued

<p>Moderate Neutropenia (500 to 999/μL)*</p>	<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
<p>Severe Neutropenia (less than 500/μL)*</p>	<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 <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

* 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

- Monitor ANC in any patient reporting a fever (temperature of 38.5°C or 101.3°F or greater) during the 2 weeks after discontinuation
- Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea
- For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for general population patients until their ANC is greater than or equal to 1500/ μ L and for patients with documented BEN until their ANC is greater than or equal to 1000/ μ L or above their baseline

Refer to Section 2.4 of the clozapine Prescribing Information for further information.

Can a patient be rechallenged with clozapine?

Yes; for some patients who experience, or have experienced, moderate clozapine-related neutropenia (ANC less than 1000/ μ L) or severe clozapine-related neutropenia (ANC less than 500/ μ L), the risk of serious psychiatric illness from discontinuing clozapine may be greater than the risk of rechallenge. This may be relevant for patients with severe schizophrenic illness who have no treatment option other than clozapine.

In making the decision to rechallenge a patient, consider:

- A hematology consult
- The ANC ranges defined in the Prescribing Information
- The patient's medical and psychiatric history
- A discussion with the patient and his or her caregiver about the benefits and risks of clozapine rechallenge
- The severity and characteristics of the neutropenic episode

Refer to Section 2.5 in the clozapine Prescribing Information for more information on how to restart clozapine in patients who have discontinued clozapine.

3 Clozapine REMS Program Requirements for Prescribers

What is the role of prescribers in the Clozapine REMS Program?

Step 1: Review the Prescribing Information for clozapine

Step 2: Certify* in the Clozapine REMS Program by:

-  Reviewing *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
-  Passing the *Clozapine REMS Knowledge Assessment for Healthcare Providers*
-  Completing the *Clozapine REMS Prescriber Enrollment Form*

Step 3: Enroll every new patient in the Clozapine REMS Program

Step 4: Counsel each patient (or their caregiver) about the risk of severe neutropenia which can lead to serious infection and death

Step 5: Check the ANC for each patient according to the monitoring requirements

Step 6: Submit each ANC for each patient to the Clozapine REMS Program within 7/15/31 days of the lab draw date according to the patient's monitoring frequency on file with the Clozapine REMS Program

Step 7: Provide authorization to continue treatment, if necessary, through the Clozapine REMS Program when the patient's ANC results meet criteria for interruption of therapy and you decide to continue clozapine treatment

Refer to the section titled, "What is a *Treatment Rationale*?" on [page 14](#) for more details on how to authorize a patient to continue treatment.



Prescribers may designate other healthcare providers or office staff to enroll patients and enter ANC results on the prescriber's behalf.

 Find more information about designees at www.clozapinerems.com

*Prescribers who prescribe clozapine only to patients receiving inpatient medical care and other related services for surgery, acute medical conditions or injuries (usually for a short-term illness or condition) are not required to certify in the Clozapine REMS Program. Patients in this setting are required to be enrolled in the Clozapine REMS Program in order to receive clozapine. If a patient in this setting is not enrolled, he/she must be enrolled by a certified prescriber before being allowed to receive clozapine.

What do I tell my patients about clozapine?

Use the patient counseling tool entitled, *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia*. Review this information with patients or their caregivers as often as needed to ensure they understand the risk of neutropenia associated with clozapine and the importance of ANC monitoring. Refer to Section 17 (Patient Counseling Information) of the clozapine Prescribing Information for additional important counseling messages for your clozapine patients.

You may choose not to provide *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia* to the patient or caregiver if you determine that the patient's adherence to clozapine treatment will be negatively impacted by providing it.

How do I enroll a patient?

You can enroll a patient in one of two ways:

-  By signing in to the Clozapine REMS Program Website at www.clozapinerems.com and enrolling the patient online
-  By downloading a *Clozapine REMS Patient Enrollment Form* from the Clozapine REMS Program Website at www.clozapinerems.com and faxing the completed form to 844-404-8876

Complete a Clozapine REMS Patient Enrollment Form if:

- The patient has never been treated with clozapine before; or,
- If you have never treated this patient with clozapine, regardless of the patient's history of clozapine treatment

What if my patient has been treated with clozapine before?

If you have treated the patient with clozapine after **October 1, 2012**, and that patient was registered in any of the individual clozapine patient registries, the patient is listed in the Clozapine REMS Program where you can access the patient's profile.

Patient information before **October 1, 2012**, was not transferred into the Clozapine REMS Program, unless the patient was listed in the National Non-Rechallenge Master File (NNRMF).

If another prescriber has previously treated the patient with clozapine, you must enroll the patient by completing and submitting the *Clozapine REMS Patient Enrollment Form* to the Clozapine REMS Program (online or by fax) to be able to access the patient's ANC history.

If you cannot find the patient, call the Clozapine REMS Program Contact Center at 844-267-8678 for assistance or to re-enroll the patient.

If you would like to inquire about a patient's previous clozapine history before enrolling the patient, please call the Clozapine REMS Program Contact Center at 844-267-8678 for assistance.

How do I find out if my patient was listed in the National Non-Rechallenge Master File (NNRMF)?

Patients were listed in the NNRMF if a patient had a WBC less than 2,000/ μ L or an ANC less than 1,000/ μ L.



All patients who were listed in the NNRMF and all their lab data were transferred into the Clozapine REMS Program. These patients are identified with a red flag in the Clozapine REMS Program at www.clozapinerems.com.

To access patient information through the Clozapine REMS Program, you must enroll the patient. If you would like to inquire about a patient's previous clozapine history before enrolling the patient, please call the Clozapine REMS Program Contact Center at 844-267-8678 for assistance.

How do I submit ANC results for my patients?

For patients in an outpatient setting:

Prescribers or their designees are responsible for submitting ANC for each prescription to the Clozapine REMS Program before clozapine can be dispensed by a pharmacy to patients treated on an outpatient or chronic basis, including but not limited to, retail drug-stores, ambulatory care pharmacies, and pharmacies dispensing to long-term care, rehabilitation facilities and prison systems.

For patients in an inpatient setting:

Pharmacists must verify the patient is enrolled in the Clozapine REMS Program before clozapine can be dispensed by a pharmacy within a facility that dispenses clozapine to patients receiving inpatient medical care and other related services for surgery, acute medical conditions or injuries (usually for a short-term illness or condition).

While you are not required to submit ANCs to the Clozapine REMS Program before clozapine can be dispensed to a patient in an inpatient setting, you (or the certified pharmacy responsible for the patient in the hospital) are encouraged to submit ANCs to the Clozapine REMS Program with a blood draw date within the patient's monitoring frequency on file with the Clozapine REMS Program.



While the patient is hospitalized, remember to monitor ANC according to the patient's ANC monitoring frequency on file with the Clozapine REMS Program.

For Prescribers in an Outpatient setting:

Prescribers or their designees must submit the ANC one of three ways:

-  By signing in to the Clozapine REMS Program Website at www.clozapinerems.com
-  By calling the Clozapine REMS Program Contact Center at 844-267-8678
-  By faxing* the ANC results to the Clozapine REMS Program at 844-404-8876

* When using the *Clozapine REMS ANC Lab Reporting Form* to submit patient ANC to the Clozapine REMS Program, prescribers can enter the Patient ID number found on the prescriber dashboard on the website. This is also known as the Patient Enrollment ID.

When should I submit a patient's ANC to the Clozapine REMS Program?

Patient ANC information should be submitted to the Clozapine REMS Program as soon as possible after the patient blood draw occurs; but, must be submitted according to the table below, which is consistent with a patient's monitoring frequency.

Monitoring Frequency	ANC Blood Draw Date
Weekly	ANC must be submitted within 7 days of the lab draw* date
Every two weeks	ANC must be submitted within 15 days of the lab draw* date
Monthly after 12 months	ANC must be submitted within 31 days of the lab draw* date

*Assumes the lab draw date is day 0

Prescribers must ensure their patients are on the appropriate monitoring frequency and adhere to the corresponding blood draw dates in order for their patient to receive clozapine.

How do I authorize continuation of clozapine when my patient's ANC is less than 1000/ μ L (general population) or less than 500/ μ L (patients with BEN)?

When a patient's ANC is less than 1000/ μ L (general population) or less than 500/ μ L (patients with documented BEN), a prescriber may provide a *Treatment Rationale* to authorize clozapine treatment to continue.

What is a Treatment Rationale?

An authorization called a *Treatment Rationale* requires the prescriber to confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia.

How can I provide a Treatment Rationale?

- The Clozapine REMS Program will alert the prescriber if an ANC is submitted that is below the recommended thresholds for a patient; clozapine will not be dispensed to the patient unless the prescriber provides a *Treatment Rationale* to authorize continuation of treatment.
- The Clozapine REMS Program will change the treatment status automatically of a patient with a low ANC to "interrupted" or "discontinued", according to the recommendations in the Prescribing Information, found in [Table 1](#) above.

- If the prescriber wishes to continue clozapine treatment, the prescriber must change the patient's treatment status to "active", and confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (i.e., by providing a *Treatment Rationale*).

Prescribers must confirm treatment continuation one of two ways:



By signing in to the Clozapine REMS Program Website at www.clozapinerems.com and providing a *Treatment Rationale* online



By faxing a signed *Clozapine REMS ANC Lab Reporting Form* to 844-404-8876 with a completed *Treatment Rationale* section

- After the prescriber provides the *Treatment Rationale*, the Clozapine REMS Program will issue a PDA which allows the outpatient pharmacy to dispense clozapine.
- Information provided in the Clozapine REMS Program is not a substitute for appropriate documentation in the patient's medical record regarding the prescriber's decision to continue, interrupt, or discontinue clozapine treatment.

What if my clozapine patient is under hospice care?

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every six months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychiatric symptoms and the patient's terminal illness.

4 Clozapine REMS Program Requirements for Pharmacies

What types of pharmacies must be certified?

All inpatient and outpatient pharmacies must certify in the Clozapine REMS Program to purchase and dispense clozapine. The requirements for outpatient pharmacies are different from the requirements for inpatient pharmacies. The different requirements are explained in the section, "[How do I verify the patient is authorized to receive clozapine?](#)"

An **inpatient pharmacy** is a pharmacy within a facility dispensing clozapine only to patients receiving inpatient medical care and other related services for surgery, acute medical conditions or injuries (usually for a short-term illness or condition).

An **outpatient pharmacy** is a pharmacy that dispenses clozapine only to patients treated on an outpatient or chronic basis including, but not limited to, retail drug-stores, ambulatory care pharmacies, and pharmacies dispensing to long-term care, rehabilitation facilities and prison systems.

The designated authorized representative for the pharmacy will complete the *Clozapine REMS Inpatient Pharmacy Enrollment Form* and/or the *Clozapine REMS Outpatient Pharmacy Enrollment Form*. This form is to certify a single inpatient or a single outpatient pharmacy location.

- **For outpatient pharmacies**, the authorized representative must confirm if your pharmacy management system can or cannot support electronic communication with the Clozapine REMS Program to verify the Clozapine REMS Program safe-use requirements
- **For inpatient pharmacies**, a pharmacy management system that supports electronic communication with the Clozapine REMS Program is not needed

The authorized representative for the pharmacy or pharmacies can certify the pharmacy online or by fax. Certifying multiple pharmacy locations must be completed online.

Who is an Authorized Representative?

In general, an authorized representative for a pharmacy:

- Coordinates the activities required in the Clozapine REMS Program
- Establishes and implements processes and procedures to ensure compliance with the safe-use conditions required in the Clozapine REMS Program

Specific duties of an authorized representative are noted in the section, "[What is the role of the pharmacy authorized representative in the Clozapine REMS Program?](#)"

Clozapine and the Risk of Neutropenia:

A Guide for Healthcare Providers

For a pharmacy with a single location, the authorized representative may be a:

- Pharmacy Manager, or
- Staff Pharmacist

If your pharmacy has more than one pharmacy location and your organization would like to coordinate staff training and implement processes for all the pharmacies in your organization, the authorized representative may be a:

- Director of Pharmacy Services, or
- Corporate Executive overseeing Pharmacy Services

What is a Predispose Authorization (PDA)?

Before clozapine can be dispensed to a patient by a pharmacy dispensing clozapine to patients treated on an **outpatient or chronic basis**, including, but not limited to, retail drug-stores, ambulatory care pharmacies, and pharmacies dispensing to long-term care, rehabilitation facilities and prison systems, the pharmacy must obtain a PDA each time from the Clozapine REMS Program. A PDA is an electronic code that indicates the Clozapine REMS Program has verified:

- Patient is enrolled in the Clozapine REMS Program
- Prescriber is certified in the Clozapine REMS Program
- Pharmacy is certified in the Clozapine REMS Program
- ANC is within acceptable range described in the Prescribing Information, or the prescriber has provided a *Treatment Rationale*
- ANC is current (i.e., submitted within 7/15/31 days prior to the PDA transaction date according to the patient's monitoring frequency on file with the Clozapine REMS program)



Once a PDA is obtained, the outpatient pharmacy can dispense clozapine to the patient.

Obtain a PDA in one of three ways:

-  By enabling your pharmacy management system to support electronic communication with the Clozapine REMS Program
-  By using the Clozapine REMS Program Website at www.clozapinerems.com
-  By calling the Clozapine REMS Program Contact Center at 844-267-8678

Note: Inpatient pharmacies are not required to obtain a PDA. Inpatient pharmacies must complete an *Eligibility Check* for each patient before dispensing clozapine. For additional details about the *Eligibility Check*, please refer to the *Clozapine REMS Eligibility Check Fact Sheet*, or visit the Clozapine REMS Program Website at www.clozapinerems.com.

What is the role of the pharmacy authorized representative in the Clozapine REMS Program?

Designate an authorized representative for your pharmacy. The authorized representative for every pharmacy must:

Step 1: Review the Prescribing Information for clozapine

Step 2: Certify in the Clozapine REMS Program by:

-  Reviewing *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
-  Passing the *Clozapine REMS Knowledge Assessment for Healthcare Providers*
-  Completing the *Clozapine REMS Inpatient Pharmacy Enrollment Form* and/or the *Clozapine REMS Outpatient Pharmacy Enrollment Form*

Step 3: Ensure training for all relevant staff involved in the dispensing of clozapine on the Clozapine REMS Program requirements

Step 4: Put processes and procedures in place to ensure pharmacy staff obtain a PDA (for outpatient pharmacies) or conduct an *Eligibility Check* (for inpatient pharmacies) to verify that it is safe to dispense clozapine

Step 5: Renew certification in the Clozapine REMS Program every two years from initial enrollment to maintain certification to order and dispense clozapine

In addition, the authorized representative of a pharmacy that uses electronic telecommunication verification must:

- Ensure the pharmacy enables its pharmacy management system to support electronic communication with the Clozapine REMS Program
- Run the verification test transactions to ensure system connectivity

How do I verify the patient is authorized to receive clozapine?

How you verify the patient is authorized to receive clozapine depends on your pharmacy type (outpatient or inpatient) and your pharmacy's telecommunication capabilities.



Dispensing Information for All Outpatient Pharmacies

- The amount of clozapine that can be dispensed depends on when the patient's next blood draw is scheduled to occur according to the monitoring frequency requirements.
- Pharmacies should dispense enough medication to treat the patient with clozapine until the next blood draw/ANC or as directed by the prescriber.
- If you do not receive a PDA, you will receive a message explaining why you are not authorized to dispense clozapine to the patient.
- If a PDA is not received because a patient's prescriber is not certified in the Clozapine REMS Program, certified pharmacies can apply clinical judgment and provide a "Dispense Rationale" to dispense clozapine.

Outpatient Pharmacies WITH Electronic Telecommunication Verification

Certification

As part of certification in the Clozapine REMS Program, the authorized representative for your pharmacy must implement processes to comply with program requirements, which include how your pharmacy will ensure a PDA is obtained each time a clozapine prescription is dispensed.

Dispensing

Before you dispense clozapine to each patient, you must:

Step 1: Obtain a PDA using the pharmacy management system



All prescriptions require a PDA prior to dispensing, including those paid for in cash and/or not using insurance for reimbursement.

Step 2: Before issuing the PDA, the Clozapine REMS Program will verify the following:

- The **prescriber is certified** in the Clozapine REMS Program
- The **patient is enrolled** in the Clozapine REMS Program
- The **outpatient pharmacy is certified** in the Clozapine REMS Program
- The **ANC is current** according to the patient's monitoring frequency on file (i.e., the most recent ANC submitted is within 7/15/31 days prior to the PDA transaction date) with the Clozapine REMS Program
- The **ANC is within an acceptable range** described in the Prescribing Information, or the prescriber has provided a *Treatment Rationale*

Step 3: Once a PDA is obtained, dispense clozapine to the patient.

- You do not need to document the PDA on the prescription or in your pharmacy management system
- If you do not receive a PDA, the Clozapine REMS Program will provide a message to explain why you are not authorized to dispense clozapine to the patient
- The pharmacist is encouraged to submit the patient's ANC to the Clozapine

REMS Program at intervals consistent with the patient's monitoring frequency, or if you have an ANC more current than the one reported in the PDA result, submit it to the Clozapine REMS Program by:

-  By signing in to the Clozapine REMS Program Website at www.clozapinerems.com
-  By calling the Clozapine REMS Program Contact Center at 844-267-8678
-  By faxing the ANC results to the Clozapine REMS Program at 844-404-8876

Outpatient Pharmacies *WITHOUT* Electronic Telecommunication Verification

Certification

As part of certification in the Clozapine REMS Program, the authorized representative for your pharmacy must implement processes to comply with program requirements, which include how your pharmacy will ensure a PDA is obtained each time a clozapine prescription is dispensed.

Dispensing

Before you dispense clozapine to each patient, you must obtain a PDA by:

Step 1: Accessing the Clozapine REMS Program in one of two ways:

-  Sign in to the Clozapine REMS Program Website at www.clozapinerems.com, or
-  Call the Clozapine REMS Program Contact Center at 844-267-8678

Step 2: Providing the following information:

- Patient Name
- Patient Date of Birth
- Prescriber
- Dispense Date
- NDC
- Days' Supply
- Quantity

Step 3: Before issuing the PDA, **the Clozapine REMS Program will verify** the following for you:

- The **prescriber is certified** in the Clozapine REMS Program
- The **patient is enrolled** in the Clozapine REMS Program
- The **outpatient pharmacy is certified** in the Clozapine REMS Program
- The **ANC is current** according to the patient's monitoring frequency on file (i.e., the most recent ANC submitted is within 7/15/31 days prior to the PDA transaction date) with the Clozapine REMS Program
- The **ANC is within an acceptable range** described in the Prescribing Information, or the prescriber has provided a *Treatment Rationale*

Step 4: Once a PDA is obtained, you can dispense clozapine to the patient.

- You do not need to document the PDA on the prescription or in your pharmacy management system
- If you do not receive a PDA, the Clozapine REMS Program will provide a message to explain why you are not authorized to dispense clozapine to the patient
- The pharmacist is encouraged to submit the patient's ANC to the Clozapine REMS Program at intervals consistent with the patient's monitoring frequency.

Inpatient Pharmacies

Certification

As part of certification in the Clozapine REMS Program, the authorized representative for your pharmacy must implement processes to comply with program requirements.

Obtaining a PDA is not required in an inpatient setting.

Dispensing

Before you dispense the first inpatient dose of clozapine to each patient, the inpatient pharmacist must complete an *Eligibility Check* as follows:

Step 1: Access the Clozapine REMS Program by:

-  Signing in to the website at www.clozapinerems.com, or
-  Calling the Clozapine REMS Program Contact Center at 844-267-8678

Step 2: Obtain an *Eligibility Check* to verify the patient is enrolled in the Clozapine REMS Program. To obtain an *Eligibility Check*, you must provide the following information:

- Pharmacy Location Information
- Patient Name
- Patient Date of Birth
- Prescriber
- Dispense Date
- NDC

Step 3: Verify the ANC is within acceptable range as described in the Prescribing Information, or the prescriber has authorized the continuation of clozapine treatment by either (a) completing an *Eligibility Check* or (b) reviewing the patient's medical record in their hospital's medical record system.

Step 4: Verify the ANC is current according to the patient's ANC monitoring frequency on file (i.e., submitted within 7/15/31 days prior to the *Eligibility Check* transaction date) with the Clozapine REMS Program by either (a) completing an *Eligibility Check* or (b) reviewing the patient's medical record in their hospital's medical record system.

The pharmacist is encouraged to submit the patient's ANC obtained at the inpatient facility to the Clozapine REMS Program at intervals consistent with the patient's monitoring frequency. ANC results may be submitted:

- ☎ By calling the Clozapine REMS Program Contact Center at 844-267-8678
- 📠 By faxing the ANC results to the Clozapine REMS Program at 844-404-8876

How does an outpatient pharmacy authorize continuation of clozapine when the patient's physician is not certified in the Clozapine REMS Program?

Outpatient pharmacies may provide a *Dispense Rationale* to dispense clozapine to a patient.

What is a Dispense Rationale?

The Clozapine REMS Program provides certified outpatient pharmacies with an opportunity to apply clinical judgment and continue to dispense clozapine to enrolled patients when a patient's prescriber is not certified in the Clozapine REMS Program. In order to dispense to a patient who does not have an associated certified prescriber, the pharmacist must provide a *Dispense Rationale*.

- The Clozapine REMS Program will alert the pharmacy if the prescriber is not certified in the Clozapine REMS Program when a PDA is requested. A PDA will not be issued for a clozapine dispense unless the pharmacy provides a *Dispense Rationale* to authorize a dispense.
- In order for a patient to be eligible for a *Dispense Rationale*, that patient must:
 - Be enrolled in the Clozapine REMS Program
 - Have an acceptable ANC value on file or, if the ANC on file is low indicating moderate or severe neutropenia, a *Treatment Rationale* must be on file
- The *Dispense Rationale* is valid for 72 hours (3 calendar days).
- The *Dispense Rationale* will be limited to no more than three (3) *Dispense Rationales* for an individual patient within a rolling six (6) month period.
- Pharmacies must fill and dispense no more than the amount of clozapine necessary to treat the patient until the next blood draw/ANC or as directed by the prescriber.

How can I provide a Dispense Rationale?

Certified authorized representatives and enrolled pharmacy staff for certified pharmacies provide the *Dispense Rationale* electronically via one of two available processes, depending on whether your pharmacy requests a *Predispense Authorization* by using the Clozapine REMS Program Website (see section A. below) or by using the pharmacy network system, i.e., "switch" (see section B. below).

A. Pharmacies using the Clozapine REMS Program Website to request a *Predispense Authorization* should:

Step 1: Log into the Clozapine REMS Program Website at www.clozapinerems.com .
Step 2: Access the dashboard.
Step 3: Select ' <i>Predispense Authorization</i> ' from the drop-down menu and click the Go button.
Step 4: Enter the patient information on the ' <i>Predispense Authorization</i> ' screen and click Submit . The ' <i>Predispense Authorization Result</i> ' screen will appear with a reject message.
Step 5: Click the ' Provide a <i>Dispense Rationale</i> for this patient ' check box at the bottom of the ' <i>Predispense Authorization Result</i> ' screen and click the Submit button.
Step 6: If the <i>Dispense Rationale</i> was provided successfully, a success screen will appear.

B. Pharmacies using the using the pharmacy network system (i.e., “switch”) to request a *Predispense Authorization* should:

Step 1: Log in to the Clozapine REMS Program Website at www.clozapinerems.com .
Step 2: Access the dashboard.
Step 3: Select ' <i>Dispense Rationale</i> ' from the drop-down menu and click the Go button.
Step 4: Enter the patient information on the <i>Dispense Rationale</i> screen and click submit .
Step 5: The " <i>Dispense Rationale Result</i> " screen will appear with a reject message similar to the switch reject message.
Step 6: Click on the ' Provide a <i>Dispense Rationale</i> for this patient ' check box at the bottom of the ' <i>Dispense Rationale Result</i> ' screen and click Submit .
Step 7: If the <i>Dispense Rationale</i> is provided successfully, a success screen will appear.
Step 8: Reprocess the claim transaction through the pharmacy switch system.
Note: Please wait approximately 2 minutes before going back to the switch to reprocess the claim transaction.

If you experience any issues, please call the Clozapine REMS Program Contact Center at 844-267-8678.

5 Reporting Adverse Events Associated with Clozapine

Report suspected adverse events directly to the Clozapine REMS Program Contact Center at 844-267-8678. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500A, available at www.fda.gov/medwatch.

6 Clozapine REMS Program Information and Resources

Additional Clozapine REMS Program information and resources are available online at www.clozapinerems.com or by calling the Clozapine REMS Program Contact Center at 844-267-8678.