

# CLOZAPINE REMS

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

## **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 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/ $\mu$ 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 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
- Fazaclo® (clozapine, USP) orally disintegrating tablets
- Versacloz® (clozapine, USP) oral suspension
- 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

- Must certify in the Clozapine REMS Program to prescribe clozapine
- Must enroll all patients in the Clozapine REMS Program
- Must report patient ANC to the Clozapine REMS Program for every prescription of clozapine

### Pharmacies

- Must certify in the Clozapine REMS Program to dispense clozapine. This includes both inpatient and outpatient pharmacies
- Must verify the prescriber is certified and the patient is enrolled, prior to dispensing clozapine
- Must verify ANC is current and acceptable for each patient, or the prescriber authorized the continuation of clozapine treatment by providing the treatment rationale, prior to dispensing clozapine

### Patients

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

## 2 ANC, Neutropenia, and Patient ANC Monitoring

### What is ANC?

ANC is the laboratory parameter for monitoring patients for clozapine-induced neutropenia. Prescribers must report 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:

$$\text{ANC} = \text{Total WBC count} \times \text{Total percentage of neutrophils}^*$$

\* neutrophil includes “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/ $\mu\text{L}$
- 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 full Prescribing Information available at [www.clozapinerems.com](http://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 been diagnosed with 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 been diagnosed with BEN, so the patient is monitored according to the correct ANC monitoring algorithm.

A few important things to know about patients diagnosed with 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 schedules for patients in the General Population as well as patients who have been diagnosed with BEN are 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 ANCs. 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/ $\mu$ L for the General Population, ANC greater than or equal to 1000/ $\mu$ L for Patients with BEN) for the first six months of therapy, monitoring frequency can be reduced to every 2 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 once every 4 weeks.

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



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

- at least 1500/ $\mu$ L for the General Population
- at least 1000/ $\mu$ L for patients diagnosed with 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
<p><b>Normal Range for a New Patient</b> <b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>ANC ≥ 1500/μL</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>≥ 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 six 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>BEN POPULATION</b></p> <ul style="list-style-type: none"> <li>ANC ≥ 1000/μL</li> <li>Obtain at least two baseline ANC levels before initiating treatment</li> </ul>		
<p><b>Mild Neutropenia</b> (1000 - 1499/μL)*</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 ≥ 1500/μL</li> <li>Once ANC ≥ 1500/μL 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>≥ 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 six 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</b> (500 - 999/μL)*</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 ≥ 1000/μL</li> </ul>	<p><b>GENERAL POPULATION</b></p> <ul style="list-style-type: none"> <li>Daily until ANC ≥ 1000/μL, then</li> <li>Three times weekly until ANC ≥ 1500/μL</li> <li>Once ANC ≥ 1500/μL 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 ≥ 1000/μL or ≥ patient's known baseline.</li> <li>Once ANC ≥ 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.**</li> </ul>
<p><b>Severe Neutropenia</b> (&lt; 500/μL)*</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 ≥ 1000/μL</li> <li>Three times weekly until ANC ≥ 1500/μL</li> <li>If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/μL</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 ≥ 500/μL</li> <li>Three times weekly until ANC ≥ patient's established baseline</li> <li>If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1000/μL or at patient's baseline</li> </ul>

\* 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

## **Can a patient continue clozapine treatment with an ANC less than 1000/ $\mu$ L?**

### **For Patients in the General Population**

Yes. Prescribers may choose to continue clozapine treatment in patients with ANCs less than 1000/ $\mu$ 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/ $\mu$ L are at risk of developing complications of severe neutropenia (including death).

Refer to Section 3 of this document for more details on how to authorize a patient to continue treatment.

### **For Patients with BEN**

Yes. The Prescribing Information for clozapine recommends interrupting clozapine treatment for patients with BEN only when the ANC is *less than 500/ $\mu$ L*. No interruption in treatment is recommended for ANC 500-999/ $\mu$ 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/ $\mu$ L, initiate appropriate neutropenia workup 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 last ANC. Abrupt treatment discontinuation is necessary for moderate to severe neutropenia that you suspect is caused by clozapine.



**REMEMBER** to report the decision to discontinue clozapine for a patient to the Clozapine REMS Program. You can do this one of three ways:



By signing into the Clozapine REMS Program website at [www.clozapinerems.com](http://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 *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 1** as shown below.

<p><b>Moderate Neutropenia</b> (500 to 999/<math>\mu</math>L)*</p>	<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> </ul>
<p><b>Severe Neutropenia</b> (less than 500/<math>\mu</math>L)*</p>	<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> </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> patients established 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

- 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/ $\mu$ L and for Patients with BEN until their ANC is greater than or equal to 1000/ $\mu$ 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/ $\mu$ L) or severe clozapine-related neutropenia (ANC less than 500/ $\mu$ 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 full 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 Re-initiation of Treatment 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 full 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 *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

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

**Step 6: Report each ANC** for each patient to 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 13 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](http://www.clozapinerems.com).



#### What do I tell my patients about clozapine?

Use the patient counseling tool titled *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*. 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 of the clozapine Prescribing Information for additional important counseling messages for your clozapine patients.

You may choose not to provide *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers* 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 one of two ways:

-  By signing into the Clozapine REMS Program website at [www.clozapinerems.com](http://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](http://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's information 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) (see the following Section for a definition of the 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 access the patient's ANC history.

If you cannot find the patient, contact the REMS program at 844-267-8678 for assistance or 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 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/ $\mu$ L or an ANC less than 1,000/ $\mu$ 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](http://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 at 844-267-8678 for assistance.

## How do I report ANC results for my patients?

### For Outpatients:

Prescribers or their designees are responsible for reporting ANC for each prescription to the Clozapine REMS Program before clozapine can be dispensed.

### For Inpatients: If your patient is hospitalized...

Before dispensing clozapine to patients, pharmacists must be able to verify the ANC is current and acceptable for each patient, or the prescriber has authorized the continuation of clozapine treatment by providing a "treatment rationale."

While you are not required to submit ANCs to the Clozapine REMS Program before clozapine can be dispensed to an inpatient, you (or the certified pharmacy responsible for the patient in the hospital) must submit ANCs to the Clozapine REMS Program within 7 days of the blood draw.



While the patient is hospitalized, remember to monitor ANC according to the patient's ANC monitoring frequency.

### For both Inpatients and Outpatients:

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

- By signing in to the Clozapine REMS Program website at [www.clozapinerems.com](http://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

## How do I authorize continuation of clozapine when my patient's ANC is less than 1000/ $\mu$ L (General Population) or less than 500/ $\mu$ L (Patients with BEN)?



### What is a treatment rationale?

When a patient's ANC is less than 1000/ $\mu$ L (General Population) or less than 500/ $\mu$ L (Patients with BEN), a prescriber may authorize clozapine treatment to continue. This 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 do I report a treatment rationale?

- The Clozapine REMS Program will alert the prescriber if an ANC is provided 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 continued treatment
- 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, 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., the 'treatment rationale')

Prescribers must confirm treatment continuation one of two ways:

-  By signing into the Clozapine REMS Program website at [www.clozapinerems.com](http://www.clozapinerems.com)
-  By faxing a signed *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 Predispose Authorization (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 Section “What are the requirements for different pharmacy types?”

The designated authorized representative for the pharmacy will complete the *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 done online.

## What 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 pharmacies in the Clozapine REMS Program?"

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

- Pharmacy Manager
- 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
- Corporate Executive overseeing Pharmacy Service

## What is a Predispense Authorization (PDA)?

Before dispensing clozapine to an **outpatient**, the pharmacy must obtain a Predispense Authorization, or PDA, 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 current (reported within 7 days of the blood draw)
- ANC is within an acceptable range, or the prescriber provided a treatment rationale



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 signing into Clozapine REMS Program website at [www.clozapinerems.com](http://www.clozapinerems.com)
-  By calling the Clozapine REMS Program contact center at 844-267-8678







Inpatient pharmacies are not required to obtain a PDA before dispensing clozapine.

### What is the role of pharmacies in the Clozapine REMS Program?

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

**Step 1: Review the full 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 *Knowledge Assessment for Healthcare Providers*
-   Completing the *Clozapine REMS 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 verify:**

- The prescriber is certified in the Clozapine REMS Program prior to dispensing clozapine
- The patient is enrolled in the Clozapine REMS Program prior to dispensing clozapine
- The ANC is current (reported within 7 days of the blood draw) and acceptable according to the patient's monitoring schedule, or the prescriber has provided a treatment rationale to authorize the continuation of clozapine treatment

**Step 5: Renew certification** in the Clozapine REMS Program every 2 years from initial enrollment

### 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 and your pharmacy's telecommunication capabilities.

## Outpatient Pharmacies WITH Electronic Telecommunication Verification

### Certification

As part of certification in the Clozapine REMS Program, an authorized representative for the pharmacy must:

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

### Dispensing

Before you dispense clozapine to each patient, you must:

- Process all clozapine prescriptions through the pharmacy management system to obtain a PDA
- Obtain a PDA. The PDA indicates that:
  - the prescriber is certified,
  - the patient is enrolled, and
  - the ANC for the patient is current and acceptable according to the patient's monitoring schedule, or the prescriber has authorized the continuation of clozapine treatment

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



#### Dispensing Information for **All Pharmacies**

- The amount of clozapine that can be dispensed depends on when the patient's next blood draw is, according to the monitoring 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



## 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 for each clozapine prescription dispensed.

### Dispensing

Obtain a PDA in one of two ways:

-  By signing into Clozapine REMS Program website at [www.clozapinerems.com](http://www.clozapinerems.com)
-  By calling the Clozapine REMS Program contact center at 844-267-8678

To obtain a PDA, you must provide the following information to the Clozapine REMS Program:

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

The Clozapine REMS Program will verify the following for you and issue a PDA:

- The prescriber is certified in the Clozapine REMS Program
- The patient is enrolled in the Clozapine REMS Program
- The ANC is current and acceptable according to the patient's monitoring schedule, or the prescriber has authorized the continuation of clozapine treatment

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 explain why you are not authorized to dispense clozapine to the patient.

## 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.

### Dispensing

Obtaining a PDA is not required in an inpatient setting.

**Before you dispense clozapine for the first time** to each inpatient, the inpatient pharmacist must:

**Step 1: Access the Clozapine REMS Program** by:

-  Signing into the website at [www.clozapinerems.com](http://www.clozapinerems.com), or
-  Calling the Clozapine REMS Program contact center at 844-267-8678




**Step 2: Provide the following information:**

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

**Step 3: Verify patient eligibility** to receive clozapine by:

- Verifying the prescriber is certified in the Clozapine REMS Program
- Verifying the patient is enrolled in the Clozapine REMS Program

**Step 4: Verify that the ANC is current and acceptable** according to the patient's ANC monitoring schedule, or the prescriber has authorized the continuation of clozapine treatment by:

-  Signing into the website at [www.clozapinerems.com](http://www.clozapinerems.com),
-  Calling the Clozapine REMS Program contact center at 844-267-8678, or
-  Reviewing the patient's medical record in their hospital's medical record system

**Throughout the patient's hospitalization:** In accordance with the patient's ANC monitoring schedule, continue to verify that the ANC is current and acceptable (or the prescriber has authorized the continuation of clozapine treatment) using one of the ways listed above.

## 5 Reporting Adverse Events Associated with Clozapine

Report suspected adverse events directly to the Clozapine REMS Program 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](http://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](http://www.clozapinerems.com) or by contacting the Clozapine REMS Program contact center at 844-267-8678.

Please select the best answer for each of the following questions. All questions must be answered correctly to become certified:

**Question 1**

All clozapine products are only available under the shared Clozapine REMS Program.

- A. True
- B. False

**Question 2**

Clozapine is associated with severe neutropenia.

- A. True
- B. False

**Question 3**

Severe neutropenia is defined as:

- A. A white blood cell count (WBC) less than 2000/ $\mu$ L
- B. An absolute neutrophil count (ANC) less than 1000/ $\mu$ L
- C. An absolute neutrophil count (ANC) less than 500/ $\mu$ L
- D. None of the above

**Question 4**

Before initiating treatment with clozapine:

- A. A baseline absolute neutrophil count (ANC) must be at least 1000/ $\mu$ L for a patient with documented Benign Ethnic Neutropenia (BEN)
- B. A baseline absolute neutrophil count (ANC) must be at least 1500/ $\mu$ L for a patient who is part of the General Population (i.e., the patient does not have BEN)
- C. A baseline absolute neutrophil count (ANC) is not necessary
- D. Both A and B

**Question 5**

Before clozapine is dispensed to a patient, a prescriber must:

- A. Determine if the patient has Benign Ethnic Neutropenia (BEN)
- B. Enroll the patient in the Clozapine REMS Program
- C. Counsel the patient/caregiver about the risk of severe neutropenia
- D. Order blood work to obtain an ANC
- E. Review the ANC and provide it to the Clozapine REMS Program
- F. All of the above

If you plan on faxing this Knowledge Assessment to the Program please provide your NPI so we can associate your progress with your stakeholder record. You can provide this information below.

Name: \_\_\_\_\_ NPI: \_\_\_\_\_ Fax: \_\_\_\_\_

**Question 6**

For outpatients, prescribers must report the ANC to the shared Clozapine REMS Program before the patient can be dispensed clozapine.

- A. True
- B. False

**Question 7**

Before clozapine can be dispensed, a pharmacist must:

- A. Verify the prescriber is certified in the shared Clozapine REMS Program
- B. Verify the patient is enrolled in the shared Clozapine REMS Program
- C. For outpatients - verify the ANC is acceptable or verify the prescriber authorized continuing treatment if the ANC is abnormal by obtaining a pre-dispense authorization from the Clozapine REMS Program
- D. For inpatients - verify the ANC is acceptable or verify the prescriber authorized continuing treatment if the ANC is abnormal by accessing the Clozapine REMS Program or by accessing the ANC through the hospital's medical record system
- E. All of the above

**Question 8**

How much clozapine can be dispensed?

- A. A 30 day supply
- B. A 90 day supply
- C. As much as the patient wants or the insurance will pay for
- D. It depends when the patient's next blood draw is according to the monitoring requirements. Dispense enough medication to treat the patient with clozapine until the next blood draw/ANC or as directed by the prescriber

**Question 9**

Regarding patients with benign ethnic neutropenia (BEN), which of the following statements are true?

- A. Patients with BEN have a different clozapine treatment algorithm and monitoring requirements
- B. Patient with BEN are healthy and do not suffer from repeated severe infections
- C. Patients with BEN are NOT at increased risk for developing clozapine-induced neutropenia
- D. Before starting clozapine, additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Hematology consultation may be necessary
- E. All of the above statements are true

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**Question 10**

If a new patient's baseline ANC is within the normal range, how should the ANC monitoring schedule proceed?

- A. Weekly from initiation to discontinuation of therapy
- B. Weekly from initiation to 6 months; every 2 weeks from 6 to 12 months; monthly after 12 months
- C. Monthly from initiation to discontinuation of therapy
- D. No additional ANC monitoring is required if the patient's baseline ANC is within the normal range

**Question 11**

If a patient's ANC indicates mild neutropenia, which of the following statements is true?

- A. ANC monitoring should be conducted three times weekly until ANC  $\geq 1500/\mu\text{L}$  if the patient is part of the General Population (i.e., if the patient does not have Benign Ethnic Neutropenia (BEN))
- B. Mild neutropenia is within the normal range for a patient with BEN
- C. If the patient has BEN, ANC monitoring should be conducted: weekly from initiation to 6 months; every 2 weeks from 6 to 12 months; monthly after 12 months
- D. All of the above

**Question 12**

If a patient's ANC indicates moderate neutropenia, which of the following statements is true?

- A. Treatment should be continued regardless of whether the patient is part of the General Population or has Benign Ethnic Neutropenia (BEN)
- B. If the patient is part of the General Population (i.e., if the patient does not have BEN), interrupt therapy and conduct ANC monitoring: daily until ANC  $\geq 1000/\mu\text{L}$ ; three times weekly until ANC  $\geq 1500/\mu\text{L}$ ; weekly for 4 weeks; then return to the patient's last "Normal Range" ANC monitoring interval
- C. The ANC monitoring schedule is the same regardless of whether the patient is part of the General Population or has BEN
- D. None of the above

**Question 13**

If a patient's ANC indicates severe neutropenia, which of the following statements is true?

- A. Treatment should be interrupted regardless of whether the patient is part of the General Population or has Benign Ethnic Neutropenia (BEN) and a hematology consultation should be considered; resume treatment only if the prescriber determines that the benefits of clozapine therapy outweigh the risks
- B. If the patient is part of the General Population (i.e., if the patient does not have BEN), interrupt treatment and conduct ANC monitoring: daily until ANC  $\geq 1000/\mu\text{L}$ ; three times weekly until ANC  $\geq 1500/\mu\text{L}$
- C. The patient may still be rechallenged with clozapine at the discretion of the prescriber
- D. All of the above

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Name: \_\_\_\_\_ NPI: \_\_\_\_\_ Fax: \_\_\_\_\_