



Clozapine and the Risk of Neutropenia:

A Guide for Pharmacists

This Guide discusses:

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



Look for this symbol to point out changes to the Clozapine REMS.

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1 The Clozapine REMS

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). 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 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
- Approved generic equivalents of these products

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

Prescribers (who prescribe clozapine for outpatient use or initiate treatment for inpatients)

- Must certify in the Clozapine REMS to prescribe clozapine
- Must enroll all patients in the Clozapine REMS
- Must provide a baseline ANC when enrolling a new patient
- Must order ANC testing for each of their clozapine patients according to the clozapine Prescribing Information
- Must verify each clozapine patient's ANCs to the Clozapine REMS monthly, using the *Patient Status Form* (Each ANC value may be separately submitted, when obtained, using the ANC Lab Reporting Form)

Outpatient Pharmacies

- Must certify in the Clozapine REMS to dispense clozapine
- Must obtain a REMS Dispense Authorization (RDA) prior to dispensing a clozapine prescription.

For the first dispensing after enrollment, the RDA will verify that:

- the pharmacy is certified
- the patient is enrolled
- the patient's treatment is not interrupted or discontinued

For a subsequent dispensing, the RDA will verify that:

- the pharmacy is certified
- the patient is enrolled
- a Patient Status Form has been completed in the last 37 days
 - the prescriber has authorized the continuation of treatment if one or more labs are missing
 - the prescriber has provided a Treatment Rationale if the most current ANC lab value is below the acceptable range
- the patient's treatment is not interrupted or discontinued



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Inpatient Pharmacies

- Must certify in the Clozapine REMS to dispense clozapine
- Must obtain a REMS Dispense Authorization (RDA) before the **initial** dispensing of clozapine.

For the first dispensing after enrollment, the RDA will verify that:

- the pharmacy is certified
- the patient is enrolled
- the patient's treatment is not interrupted or discontinued

For a subsequent dispensing, the RDA will verify that:

- the pharmacy is certified
- the patient is enrolled
- a Patient Status Form has been completed in the last 37 days
 - the prescriber has authorized the continuation of treatment if one or more labs are missing
 - the prescriber has authorized a Treatment Rationale if the most current ANC lab value is below the acceptable range
- the patient's treatment is not interrupted or discontinued

Patients

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



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

What is Absolute Neutrophil Count (ANC)?

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:

Absolute Neutrophil Count	=	Total WBC Count	X	Total percentage of neutrophils* obtained from the differential
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*Includes both banded and segmented neutrophils

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 full 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 been diagnosed with BEN have a separate ANC monitoring algorithm when treated with clozapine.

When enrolling a patient in the Clozapine REMS, 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?

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 diagnosed with BEN



During treatment, monitor ANC regularly as described in [Table 1](#) and [Table 2](#) below.

Patients may transition to less frequent ANC monitoring based on the number of weeks of continuous clozapine therapy and the patient's ANC's.

During the first six months of treatment:

- Weekly ANC monitoring is required for all patients

During the second six months of treatment:

- Monitoring frequency can be reduced to every two weeks 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)

After one year of treatment:

- If the patient's ANC continues to remain in the normal range, ANC monitoring may be reduced to monthly (every 4 weeks) thereafter.

The recommended ANC monitoring frequency for patients in the general population and patients who have documented BEN is shown in **Table 1** and **Table 2** below. The table also provides recommendations for monitoring patients who experience a decrease in ANC during the course of treatment.

Table 1 - Recommended Monitoring Frequency and Clinical Decisions by ANC Level for the General Patient Population

ANC Level	Treatment Recommendation	ANC Monitoring
Normal Range ANC \geq 1500/ μ L	<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)*	<ul style="list-style-type: none"> • Continue treatment 	<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**
Moderate Neutropenia (500 - 999/ μ L)*	<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 	<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**
Severe Neutropenia (< 500/ μ L)*	<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 	<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

* Confirm all initial reports of ANC less than 1500/ μ L with a repeat ANC measurement within 24 hours

** If clinically appropriate

Table 2 - Recommended Monitoring Frequency and Clinical Decisions by ANC Level for Patients with BEN

ANC Level	Treatment Recommendation	ANC Monitoring
Normal BEN Range (Established ANC baseline $\geq 1000/\mu\text{L}$)	<ul style="list-style-type: none"> 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 ≥ 30 days, monitor as if new patient Discontinuation for reasons other than neutropenia 	<ul style="list-style-type: none"> Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months See Section 2.4 of the Prescribing Information
BEN Neutropenia (500 - 999/ μL)*	<ul style="list-style-type: none"> Recommend hematology consultation Continue treatment 	<ul style="list-style-type: none"> Three times weekly until ANC $\geq 1000/\mu\text{L}$ or \geq patient's known baseline. Once ANC $\geq 1000/\mu\text{L}$ or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**
BEN Severe Neutropenia ($< 500/\mu\text{L}$)*	<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 	<ul style="list-style-type: none"> Daily until ANC $\geq 500/\mu\text{L}$ Three times weekly until ANC \geq patient's baseline If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC $\geq 1000/\mu\text{L}$ or at patient's baseline

* Confirm all initial reports of ANC less than 1500/ μL with a repeat ANC measurement within 24 hours

** If clinically appropriate

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

For Patients in the General Population

Yes; prescribers may choose to continue clozapine treatment in patients with ANCs less than 1000/ μL . 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/ μL are at risk for developing complications of severe neutropenia, including serious infection and death.

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/ μL** . No interruption in treatment is recommended for ANC 500-999/ μL , 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** and **Table 2** 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 the prescriber suspects is caused by clozapine. The prescriber may discontinue treatment by the methods listed below.



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



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



By calling the Clozapine REMS Contact Center at 888-586-0758



By completing the "Patient Status" section of the *Clozapine REMS Patient Status Form* and faxing it to the Clozapine REMS at 800-878-5927

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

- 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

After **discontinuing** clozapine, monitor ANC according to the recommendations in **Table 3** as shown below.

Table 3 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

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 Requirements for Pharmacies

What types of pharmacies must be certified?

All inpatient and outpatient pharmacies must certify in the Clozapine REMS 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 *Inpatient Pharmacy Enrollment Form* and/or the *Outpatient Pharmacy Enrollment Form*. This form is to certify a single inpatient or a single outpatient pharmacy location.

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

Specific duties of an authorized representative are noted in the section, "**What is the role of the pharmacy authorized representative in the Clozapine REMS?**"

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 the role of the pharmacy authorized representative in the Clozapine REMS?

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

Step 1: Certify in the Clozapine REMS by:

-  Reviewing *Clozapine and the Risk of Neutropenia: A Guide for Pharmacists*
-  Successfully complete and submit the *Knowledge Assessment for Pharmacies*
-  Complete and submit the *Inpatient Pharmacy Enrollment Form* and/or the *Outpatient Pharmacy Enrollment Form*

Step 2: Ensure training for all relevant staff involved in the dispensing of clozapine on the Clozapine REMS requirements using the *Clozapine and the Risk of Neutropenia: A Guide for Pharmacists*

Once a staff is trained on the Clozapine REMS requirements, the authorized representative may invite that staff to become enrolled in the Clozapine REMS. To invite a staff or an additional authorized representative, log into your account at www.clozapinerems.com. Select the Manage Personnel button, then select the Add Authorized Representative or Staff button and follow the steps.

Step 3: Put processes and procedures in place to verify an available, current ANC is within the acceptable range for patients enrolled but not authorized to receive the drug.

For patients enrolled but not authorized to receive clozapine, verify an available, current ANC is within the acceptable range through the processes and procedures established as a requirement of the Clozapine REMS, document and submit the ANC and the prescriber's NPI to the Clozapine REMS and obtain authorization to dispense each prescription by contacting the Clozapine REMS program to verify the patient is now authorized to receive clozapine.

Does a Pharmacy's Certification Expire?

A pharmacy's certification does not expire. However, if a pharmacy's authorized representative changes, the new authorized representative must certify the pharmacy in the REMS Program by reviewing *Clozapine and the Risk of Neutropenia: A Guide for Pharmacists*, successfully completing the Knowledge Assessment for Pharmacies and the Outpatient Pharmacy Enrollment Form and submitting both to the REMS Program.

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

Before any pharmacy dispenses clozapine to a patient, you must obtain authorization from the Clozapine REMS in the form of a REMS Dispense Authorization (RDA).

What is a REMS Dispense Authorization (RDA)?

An RDA is an electronic code that indicates the Clozapine REMS has verified that all safe use conditions have been met.

For the first dispensing, the RDA will verify that:

- the pharmacy is certified
- the patient is enrolled
- the patient's treatment is not interrupted or discontinued

For a subsequent dispensing, the RDA will verify that:

- the pharmacy is certified
- the patient is enrolled
- a Patient Status Form has been completed in the last 37 days
 - the prescriber has authorized the continuation of treatment if one or more labs are missing
 - the prescriber has provided a Treatment Rationale if the most current ANC lab value is below the acceptable range
 - the patient's treatment is not interrupted or discontinued

Obtain an RDA in one of two ways:

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By using the Clozapine REMS Website at www.clozapinerems.com



By calling the Clozapine REMS Contact Center at 888-586-0758

Outpatient Pharmacies



Certification

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

Dispensing

Before you dispense clozapine to each patient, you must obtain an RDA by:

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

-  Sign in to the Clozapine REMS Website at www.clozapinerems.com, or
-  Call the Clozapine REMS Contact Center at 888-586-0758

Step 2: Providing the following information:

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

Step 3: Before issuing the RDA, the Clozapine REMS will verify the following for you:

For the first dispensing after patient enrollment:

- the pharmacy is certified
- the patient is enrolled
- the patient's treatment is not interrupted or discontinued

For a subsequent dispensing:

- the pharmacy is certified
- the patient is enrolled
- a Patient Status Form has been completed in the last 37 days
 - the prescriber has authorized the continuation of treatment if one or more labs are missing
 - the prescriber has provided a Treatment Rationale if the most current ANC lab value is below the acceptable range
 - the patient's treatment is not interrupted or discontinued

Using a Dispense Rationale

If a Patient Status Form has not been completed within the last 37 days, a Dispense Rationale will be automatically presented to you. To use the Dispense Rationale, you must be in possession of a current ANC within an acceptable range for the patient.

Enter the prescriber's NPI number, the blood draw date, and the ANC value and select the 'Request Dispense Rationale' button.

Three Dispense Rationales may be used per patient per year.



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Step 4: Once an RDA is obtained, you can dispense clozapine to the patient.

- You do not need to document the RDA on the prescription or in your pharmacy management system
- If you do not receive an RDA, the Clozapine REMS will provide a message to explain why you are not authorized to dispense clozapine to the patient



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 an RDA, you will receive a message explaining why you are not authorized to dispense clozapine to the patient.

How do I Reverse an RDA?

If a prescription is not dispensed to the patient and is returned to stock, the RDA must be reversed. To reverse an RDA, log into your account at www.clozapinerems.com and select the Reverse RDA button. Find the patient and follow the directions.

You may also reverse an RDA by calling the Clozapine REMS Contact Center at 888-586-0758.

RDA Fact Sheet for Outpatient Pharmacies

An RDA Fact Sheet for Outpatient Pharmacies has been developed as a reference to help outpatient pharmacy staff understand the possible outcomes of an RDA, and actions to be taken by the pharmacy for each outcome. The Fact Sheet also has information for the following:

1. How Do I Request a REMS Dispense Authorization?
2. How Do I Request a Dispense Rationale?
3. How Do I Submit ANC Labs?

The RDA Fact Sheet for Outpatient Pharmacies can be found online at www.clozapinerems.com.

Inpatient Pharmacies

Certification

As part of certification in the Clozapine REMS, the authorized representative for your pharmacy must implement processes to comply with program requirements, which include how your pharmacy will ensure an RDA is obtained before the first inpatient clozapine prescription is dispensed.

Dispensing

Before you dispense the first inpatient clozapine dose to each patient, you must obtain an RDA by:

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

-  Sign into the website at www.clozapinerems.com, or
-  Call the Clozapine REMS Contact Center at 888-586-0758

Step 2: Providing the following information:

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

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

For the first dispensing after patient enrollment:

- the pharmacy is certified
- the patient is enrolled
- the patient's treatment is not interrupted or discontinued

For a subsequent dispensing:

- the pharmacy is certified
- the patient is enrolled
- a Patient Status Form has been completed in the last 37 days
 - the prescriber has authorized the continuation of treatment if one or more labs are missing
 - the prescriber has provided a Treatment Rationale if the most current ANC lab value is below the acceptable range
 - the patient's treatment is not interrupted or discontinued

Using a Dispense Rationale

If a Patient Status Form has not been completed within the last 37 days, a Dispense Rationale will be automatically presented to you. To use the Dispense Rationale, you must be in possession of a current ANC within an acceptable range for the patient.

Enter the blood draw date and the ANC value and select the 'Request Dispense Rationale' button.



New

Step 4: Once an RDA is obtained, you can dispense clozapine to the patient.

- You do not need to document the RDA on the prescription or in your pharmacy management system
- If you do not receive an RDA, the Clozapine REMS will provide a message to explain why you are not authorized to dispense clozapine to the patient



While the patient is hospitalized, we encourage reporting ANC values to the Clozapine REMS according to the patient's monitoring frequency using one of the options below.

How Do I Submit ANC values Outside of the RDA Process?

Yes, ANC values can be submitted using the following options:

Option 1: Use the Clozapine REMS Website to:

1. Log in to your account at www.clozapinerems.com
2. Select the button 'Submit ANC Lab'
3. Find the patient information and enter the ANC value and Blood Draw Date

Option 2: Document the ANC results on an ANC Lab Reporting Form and fax the completed form to 800-878-5927.

Option 3: Call the Clozapine REMS Contact Center at 888-586-0758.

How do I Reverse an RDA?

If a prescription is not dispensed to the patient and is returned to stock, the RDA must be reversed. To reverse an RDA, log into your account at www.clozapinerems.com and select the Reverse RDA button. Find the patient and follow the directions.

You may also reverse an RDA by calling the Clozapine REMS Contact Center at 888-586-0758.

RDA Fact Sheet for Inpatient Pharmacies

An RDA Fact Sheet for Inpatient Pharmacies has been developed as a reference to help inpatient pharmacy staff understand the possible outcomes of an RDA, and actions to be taken by the pharmacy for each outcome. The Fact Sheet also has information for the following:

1. How Do I Request a REMS Dispense Authorization?
2. How Do I Request a Dispense Rationale?
3. How Do I Submit ANC Labs?

The RDA Fact Sheet for Inpatient Pharmacies can be found online at www.clozapinerems.com.

4 Reporting Adverse Events Associated with Clozapine

Report suspected adverse events directly to the Clozapine REMS Contact Center at 888-586-0758. 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.

5 Clozapine REMS Information and Resources

Additional Clozapine REMS information and resources are available online at www.clozapinerems.com or by calling the Clozapine REMS Contact Center at 888-586-0758.

Glossary

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.

Dispense Rationale: The Clozapine REMS Program provides certified pharmacies with an opportunity to apply clinical judgment and continue to dispense clozapine to enrolled patients when a Patient Status Form has not been received and the pharmacist is in possession of a current ANC within an acceptable range for the patient.

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 drugstores, ambulatory care pharmacies, and pharmacies dispensing to long-term care, rehabilitation facilities and prison systems.

REMS Dispense Authorization (RDA): An authorization given to pharmacies which reflects that the safe-use conditions for that patient have been met. The RDA is provided by the Clozapine REMS. For an outpatient pharmacy, the RDA verifies that the patient is enrolled, the pharmacy is certified, and that the patient is authorized to receive drug. For an inpatient pharmacy, the RDA verifies that the patient is enrolled, and the pharmacy is certified. This RDA 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.