

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/ μL)*	<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 patients 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.

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/ 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/μL, 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. 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/μL and for patients with documented BEN until their ANC is greater than or equal to 1000/μL or above their baseline

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

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 Prescribers

What is the role of prescribers in the Clozapine REMS?

Step 1: Review the Prescribing Information for clozapine

Step 2: Certify* in the Clozapine REMS by:

-  Reviewing *Clozapine and the Risk of Neutropenia: A Guide for Prescribers*
-  Successfully complete and submit the *Knowledge Assessment for Prescribers*
-  Complete and submit the *Prescriber Enrollment Form*

Step 3: Counsel each patient (or their caregiver) about the risk of severe neutropenia, which can lead to serious infection and death

Step 4: Enroll every new patient in the Clozapine REMS, providing an ANC with the enrollment

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

Step 6: Submit each patient's ANCs to the Clozapine REMS monthly, using the *Patient Status Form*

Step 7: Provide authorization to continue treatment, if necessary, through the Clozapine REMS 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 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. Patients in this setting are required to be enrolled in the Clozapine REMS 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.

How do I Designate a Prescriber Designee?

Prescribers may designate other healthcare providers or office staff to enroll patients and submit ANC results monthly, using the Patient Status Form, on the prescriber's behalf.

 Visit www.clozapinerems.com.

To enroll a prescriber designee online, log into your account and select the Manage Designees button. Select the Invite Designee button. Follow the instructions. The designee will receive an email with a link to allow them to create an account. Once created, the designee may log into their account and enroll patients and submit ANC results monthly, using the Patient Status Form, on your behalf.

To enroll a prescriber designee via fax, print out the Prescriber Designee Enrollment Form. Complete all sections. Both you and the designee must sign the form. Fax the form to 800-878-5927.

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* to help counseling your patients.
- Tell your patients about the risk of severe neutropenia which can lead to serious infections and death.
- Explain the importance of having required blood tests to check if a patient is more likely to get an infection.
- Tell patients to talk to a doctor immediately if they have any symptoms of infection. These symptoms are clearly laid out in the counseling tool. Provide your patient with the counseling tool.

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. If you choose to not provide the guide to a patient, remember to talk about the following symptoms:

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| • Infection, including skin, throat, urinary tract, vaginal, pneumonia, or any other infection | • Pain or burning while urinating |
| • Fever or chills | • Unusual vaginal discharge or itching |
| • Sores or ulcers inside your mouth, gums, or on your skin | • Abdominal pain |
| • Wounds that take a long time to heal | • Sores or pain in or around your rectal area |
| • Feel like you have the flu | • Feel extremely weak or tired |

How do I enroll a patient?

You can enroll a patient in one of two ways:

-  By signing into the Clozapine REMS Website at www.clozapinerems.com and enrolling the patient online
-  By downloading a *Patient Enrollment Form* from the Clozapine REMS Website at www.clozapinerems.com and faxing the completed form to 800-878-5927

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




How do I submit ANC results for my patients?

Prescribers and Prescriber Designees

Prescribers or their designees are responsible for submitting ANC monthly, using the *Patient Status Form*, to the Clozapine REMS before clozapine can be dispensed by an outpatient pharmacy.

For Prescribers in an Outpatient setting:

Submit the *Patient Status Form* monthly in one of three ways:

-  By signing into the Clozapine REMS Website at www.clozapinerems.com
-  By calling the Clozapine REMS Contact Center at 888-586-0758
-  By faxing* the *Patient Status Form* results to the Clozapine REMS at 800-878-5927

Pharmacies

Pharmacists must verify that the patient is enrolled in the Clozapine REMS and authorized to receive clozapine 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).

For patients enrolled but not authorized by the Clozapine REMS to receive clozapine, the pharmacy must verify an available, current ANC is within acceptable range through the processes and procedures established as a requirement of the Clozapine REMS, document and submit the ANC to the Clozapine REMS and obtain authorization to dispense each prescription by contacting the Clozapine REMS to verify the patient is now authorized to receive clozapine. The pharmacy may use either the ANC Reporting Form, the website, or the contact center to report an ANC.



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

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

Patient ANC information must be submitted to the Clozapine REMS using the *Patient Status Form*. Although the Patient Status Form is only submitted monthly, prescribers must ensure their patients are on the appropriate monitoring frequency and adhere to the corresponding blood draw intervals. Single ANCs may still be submitted via the ANC Lab Reporting Form.

Your options to submit ANCs are:

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1. Submit all at once via the *Patient Status Form* monthly
 2. Submit as labs are obtained via the *ANC Lab Reporting Form*

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. The Treatment Rationale is a section that is completed on the Patient Status Form.

How can I provide a Treatment Rationale?

- The Clozapine REMS 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 will automatically 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 confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia by providing a *Treatment Rationale* on the *Patient Status Form*. The completion of a *Treatment Rationale* will change the patient's treatment status back to "active."

Prescribers must confirm treatment continuation one of two ways:

-  By signing into the Clozapine REMS Website at www.clozapinerems.com and submitting a *Patient Status Form* online
-  By faxing a signed *Patient Status Form* to 800-878-5927 with a completed *Treatment Rationale* section

- After the prescriber provides the *Treatment Rationale*, the Clozapine REMS will issue an

RDA, which allows the outpatient pharmacy to dispense clozapine.

- Information provided in the Clozapine REMS 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, at a minimum, 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.

Designating a patient as a Hospice Care patient reduces the frequency of submitting a *Patient Status Form* to once every six months.

What if my patient has been treated with clozapine before?

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

If you cannot find the patient, call the Clozapine REMS Contact Center at 888-586-0758 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 Contact Center at 888-586-0758 for assistance.

To access patient information through the Clozapine REMS, 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 Contact Center at 888-586-0758 for assistance

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.