

# Clozapine REMS Program Updates

## A Guide for Prescribers and Pharmacists

SMI Adviser and NAMI would like to share important information with clinicians and pharmacists regarding reporting and treatment recommendation updates to the Clozapine Risk Evaluation and Mitigation Strategies (REMS) surveillance system.

This guide offers an overview of the Clozapine REMS program and transition to the new reporting system. It contains information on the changes now in effect, as well as what steps prescribers and pharmacists must follow to continue serving patients in their care.

Modifications to how clozapine is prescribed and monitored affect all NAMI members and the general public who receive clozapine as a part of their treatment plan. This information is being shared to prevent potentially harmful interruptions in treatment, by providing clinicians and pharmacists with information and resources to assist with the transition to the new reporting system.

The [Clozapine REMS Program](#), is a shared system developed by drug manufacturers to manage the risk of severe neutropenia, and ensure that the benefits of the drug outweigh this risk for each patient to whom it is prescribed. Since 2015, prescribers, pharmacists, patients, and distributors have been required to enroll in the REMS registry before clozapine can be dispensed.

**On July 29, 2021, the Food and Drug Administration (FDA) [approved changes](#) to the Clozapine REMS Program, and these modifications to the registry went into effect on November 15, 2021.<sup>1</sup>**

System changes for prescribers and pharmacies are summarized below, and include next steps, additional information, resources, and FAQs.

- All prescribers must recertify and reenroll in the new system.
- All patients must be reenrolled by their prescribers or prescriber designee(s).
- All dispensing pharmacies, wholesalers, and distributors must recertify or reenroll.

### Changes for Prescribers

- All patients must be entered into the new system individually. Previous system information, patient records, and lab data has not transferred and is not accessible in the new system. This means that prescribers (or designees) should review records in the current system for any data that they wish to record manually in their own records to maintain patient safety.
- A monthly [Patient Status Form](#) (PSF) has replaced the ANC Lab Reporting Form. The ANC Lab Reporting Form may still be used outside of the monthly reporting requirement, but is not a substitute for the PSF.
- At enrollment, the PSF must contain a baseline ANC level, and if applicable, designation of benign ethnic neutropenia (BEN), or a hospice designation. Lab reports sufficed for this information previously, but under the new system, the PSF must be completed monthly.

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- Each month, prescribers or their designees must use the PSF to submit ANC results, monitoring frequency, and a continuing treatment justification.
- PSFs with a treatment rationale for low ANC or missing labs, or designation of a BEN or a hospice patient, are only accepted if completed and signed by a certified prescriber.
- The PSF is also used to interrupt, discontinue, or resume treatment.
- With prescriber discretion, appropriate frequency of ANC testing, and a documented treatment rationale, patients may continue taking clozapine if:
  - They have a lower ANC count than the recommended thresholds.
  - They're experiencing mild symptoms of neutropenia.
  - They have, or previously had, moderate neutropenia.
  - The prescriber feels that the benefits of continuing clozapine treatment outweigh the risk; particularly if it is the only remaining treatment option.
- A treatment rationale **must** be provided to maintain the patient's active treatment status in the system and avoid interruption in treatment. This includes patients with benign ethnic neutropenia (BEN), who are eligible to receive clozapine with a lower range of ANC values accepted. A hematology consultation is not required to report BEN in the new system, but the patient must have a BEN designation entered.
- Updated reporting now allows for additional documentation for a continued treatment rationale, such as if labs have been missed for a month or more, or if the patient's ANC falls below current recommendations of 1000/ $\mu$ L, or lower than 500/ $\mu$ L for a BEN patient.
- For additional information on changes, please click [here](#).

“Prescribing clozapine for patients receiving inpatient care does not require prescriber certification in the Clozapine REMS if the patient is already enrolled in the program. If the patient is to be initiated on clozapine while admitted to an inpatient setting, a certified prescriber must enroll the patient in the Clozapine REMS program prior to receiving the first dose of clozapine.”<sup>1</sup>

## Next Steps for Prescribers

It is important that **prescribers enroll and obtain recertification immediately**, and that **patients are enrolled prior to the 37-day deadline, which falls on December 22, 2021**.

You will need to complete the following steps:

1. [Complete the enrollment form for Prescriber Certification](#). You will need your National Provider Identification (NPI), and Drug Enforcement Administration (DEA) prescriber numbers (this will be an optional entry field), and email address.
2. Review the [Clozapine and the Risk of Neutropenia Guide for Healthcare Providers](#).
3. Successfully complete a brief 12-question assessment, *Clozapine REMS Knowledge Assessment for Healthcare Providers*.

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4. Once successfully enrolled, authorize prescriber designees to perform routine monthly reporting on your behalf.
  - a. All designees must be enrolled in the Clozapine REMS Program prior to being able to perform duties for the prescriber. This includes reviewing the REMS requirements and confirming that they understand them.
  - b. Prescribers must manually initiate addition of designees in the new system, as designees may not initiate this request.
  - c. The Prescriber Designee Certification can be found here:  
<https://www.newclozapinerems.com/home>
5. Enroll your patients.
  - a. Complete the Patient Status Form, and include the most recent ANC results, including the date. In order to enroll a patient, you need to enter an ANC within the past 30 days.
  - b. Designees may enroll general population patients, but **not** those designated as BEN or hospice.
  - c. These can be submitted online or via fax and **must be received within 37 calendar days of the November 15th launch of the new system. This means that December 22nd is the deadline for enrollment.**

## Remember to:

- Recertify immediately
- Make sure you are enrolled prior to enrolling designees
- Make sure ANC lab work is complete before registering a patient
- Enroll all patients before December 22nd
- Update information for the Clozapine REMS Contact Center  
**Phone:** 888-586-0758 **Fax:** 800-878-5927

*As a prescriber, it is also helpful to review the next section on system changes for pharmacies. It will provide you with a better understanding of the pharmacy process and new requirements, and improve communication with dispensers. This is important should questions arise regarding a patient's clozapine prescription during the transition period.*

## Changes for Pharmacies

- When pharmacists enroll in the new Clozapine REMS Program, they must indicate whether their pharmacy is an inpatient or an outpatient pharmacy. If the pharmacy serves both inpatient and outpatient customers, **a separate enrollment is required for each type.**
- Hospital pharmacies that are designated as an inpatient pharmacy are **now restricted to dispensing only a 7-day supply of clozapine** to discharging patients. This does not apply to outpatient, or dually designated pharmacies.

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- Once enrollment is reviewed and approved, the REMS system will authorize the pharmacy to dispense clozapine with a REMS Dispense Authorization (RDA). **The RDA replaces the Predispense Authorization (PDA).**  
*This requirement has been temporarily paused due to system access issues. Abrupt discontinuation of clozapine can result in significant treatment complications. Per the FDA, health care professionals should use clinical judgment in prescribing and dispensing clozapine to patients with an ANC count within the acceptable range.*
- Pharmacies are only able to obtain the RDA through the Clozapine REMS website, or by calling the Clozapine REMS Contact Center. RDAs will not be obtained via the previously available SWITCH pharmacy management system.
- The RDA verifies that the patient is enrolled and authorized to receive clozapine. It also confirms that all data in the Patient Status Form (PSF) complies with the new standards and has been completed within 37 days of the launch of the new system (December 22nd).
- RDAs must be called in, but overrides will be allowed if a patient is enrolled, but their PSF isn't available. Pharmacists must have the National Prescriber Identification number (NPI) of the prescriber, as well as access to current ANC levels and they must submit a dispense rationale. Outpatient pharmacies can only do this three times a year per patient.
- Enrolled pharmacies are added to a searchable database of [REMS authorized dispensing pharmacies](#). Pharmaceutical companies and wholesalers are not able to fill clozapine order requests without evidence that pharmacies are enrolled in the new system.  
*This requirement has been temporarily paused due to system access issues. Abrupt discontinuation of clozapine can result in significant treatment complications. Per the FDA, health care professionals should use clinical judgment in prescribing and dispensing clozapine to patients with an ANC count within the acceptable range.*
- Updated information for the Clozapine REMS Contact Center (the old fax number will no longer be in service):  
**Phone:** 888-586-0758  
**Fax:** 800-878-5927
- For additional information on changes, please click [here](#).

## Next Steps for Pharmacies

All inpatient and outpatient pharmacies must have an authorized pharmacy representative complete the certification process immediately.

1. [Complete enrollment for Pharmacy Certification](#). You will need your National Provider Identification (NPI), and Drug Enforcement Administration (DEA) prescriber numbers (DEA number entry will be an optional field).
  - a. If your pharmacy dispenses for inpatient care, complete the **Inpatient Pharmacy Enrollment Form**.
  - b. If your pharmacy dispenses for outpatient care, complete the **Outpatient Pharmacy Enrollment Form**.
  - c. **If your pharmacy dispenses for both inpatient and outpatient care, complete both enrollment forms.**

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2. Review the [Clozapine and the Risk of Neutropenia Guide for Healthcare Providers](#).
3. Successfully complete a brief 12-question assessment, *Clozapine REMS Knowledge Assessment for Healthcare Providers*.
4. Conduct any pharmacy staff training needed to ensure program requirements are complied with, and confirm that the [pharmacy staff certification process](#) is completed for all dispensing staff.
  - a. Pharmacy Staff enroll by creating an online account.
  - b. Education is not required for enrollment but will be available after completion of enrollment.

## Clozapine REMS Program Frequently Asked Questions

### **When should providers or prescribers start to re-enroll?**

Enrollment is open for providers, designees, and pharmacies now. You are advised to complete the process immediately, to avoid interruptions in patient care.

### **Is it true that designees can only be attached to one prescriber?**

The program states that a single prescriber can have multiple designees. This function in the new system is being updated as a priority for prescribers.

### **Why is the DEA number required when clozapine is not a controlled substance?**

Clozapine is not a controlled substance, so it is unclear why the new system requests a DEA number, however it is an optional entry and not a requirement.

### **What should hospitals know?**

Make sure your hospital pharmacy registers twice — as an inpatient pharmacy, **and** as an outpatient pharmacy, so they are able to dispense to outpatient customers as well as discharging patients, without a 7-day supply limitation.

### **Why must hospital pharmacies only dispense a 7-day supply at discharge if the patient was previously on clozapine?**

A rationale for limiting the dispense amount to a week, even for patients already on clozapine, has not been provided. These restrictions create concerns for everyone — prescribers, pharmacies, patients, and their families. Particularly concerning is a likelihood of delayed prescription refills resulting in treatment interruption.

It may be necessary for prescribers to provide the patient's discharge prescription to a [REMS certified outpatient pharmacy](#) instead of the hospital pharmacy. You might also consider providing a full month's prescription that can be filled at the end of the initial 7-day supply filled by a hospital pharmacy. Remember that lab work must be updated in REMS for a prescription to be dispensed. Coordination of post-discharge care and medication access will be very important during this transition.

### **During COVID, the FDA made sudden changes to rules and restricted clinicians' ability to prescribe if they were not in compliance for updating blood work (i.e., ANC levels). Could this happen again?**

This was due to the risk of COVID exposure when obtaining blood work. New guidelines include the ability to add continuing treatment rationale on the PSF, allowing for flexibility if lab work is not readily available, within certain limits.

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## What are the current options for frequency of required lab work?

ANC monitoring frequency follows prescribing recommendations and ranges: 3 times a week (for cases with lower than required ANC levels), weekly, every 2 weeks, and monthly. Additional ANC entries are also permitted.

## Can you submit a batch of forms at the end of each month?

Yes, the PSF is required to be submitted monthly. If you prefer not to input forms on a weekly basis, be aware of overlapping dispense dates and double entry by designees.

## When will full functionality be active?

The REMS program states that full functionality is available as of November 15, 2021.

Other FAQs for the new system can be found at [www.newclozapinerems.com](http://www.newclozapinerems.com).

It is worth noting that many prescribers, pharmacists, various state mental health agencies — and NAMI — contacted the FDA and the Clozapine Product Manufacturers Group (CPMG) to request a delayed implementation date. Although REMS system users were told they could begin uploading information prior to the official launch, there have been issues with its functionality.

A deadline of 37 days from launch for all requirements to be met is a limited timeframe in the absence of pre-launch system functioning. Particularly considering that patient information and data does not transfer to the new system and must be manually reentered for every patient.

To compound this concern, the deadline of December 22nd occurs in the middle of the holiday season, which is already a time of year when services are delayed or less accessible. Any additional usage or technical issues that may arise post-launch would further impede patient care and disrupt effective treatment. This puts patients at risk of losing vital medication, resulting in psychiatric stability that can rapidly deteriorate.

Prescribers and pharmacists are encouraged to find avenues to address potential treatment interruptions before they occur, communicate with other providers about challenges experienced, and continue to contact the FDA and CPMG with concerns.

## Additional Information on Neutropenia and Benign Ethnic Neutropenia (BEN)

Neutropenia and severe neutropenia (agranulocytosis) are conditions resulting from significant drops in neutrophil counts. While rare, these occurrences have been associated with clozapine. It is believed that neutropenia, in part, is a heritable trait, and current studies appear to indicate an incidence rate of less than 1%.<sup>2,3</sup>

Benign ethnic neutropenia (BEN) is a condition found in certain ethnic groups who have an average absolute neutrophil count (ANC) value that is lower than standard laboratory ranges. People of Middle Eastern or non-Caucasian groups with dark skin are at highest risk of BEN, and it's found most often in people of African descent (25–50%).<sup>1,4</sup>

BEN occurs in otherwise healthy people who are not prone to infections yet meet traditional blood work criteria for a neutropenia diagnosis. Low ANC results in these ethnic groups have historically led to an overly cautious treatment approach that avoided the use of clozapine in individuals who would have otherwise benefitted.

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For people with BEN, the average ANC is 1500/ $\mu$ L, and a value less than 500/ $\mu$ L is indicative of severe neutropenia. Most individuals with BEN have an ANC between 1000/ $\mu$ L and 1500/ $\mu$ L yet are *not* at increased risk of infection.<sup>5</sup> This range is acceptable diagnostically, but if prescribers still have concerns, they can request a red blood cell antigen test, specifying an evaluation for the [Duffy antigen](#).<sup>6</sup> Genetic testing and hematology consultation are not necessary. Because of these updated recommendations, clozapine is a viable treatment option for people of Middle Eastern, African, or non-Caucasian descent.

## Additional Resources

- Help for navigating the Clozapine REMS Program for [first time users](#).
- The SMI Adviser's Clozapine and LAI Virtual Forum webinar, [Keeping up with Clozapine REMS: Active Clinician Discussion](#) and [A Guide to Navigating the November 15 Changes](#) are available from the American Psychiatric Association (APA).
- You can also join the [SMI Adviser's Clozapine and LAI Centers of Excellence Exchange listserv](#).
- The [Clozapine Center of Excellence](#) from [SMI Adviser](#) offers education and resources for clinicians, patients and families.
- NAMI provides [information on clozapine for patients and families](#), as well as [support groups](#) for individuals with mental health conditions, and their families.

## References

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- <sup>3</sup> Mijovic A, MacCabe JH. Clozapine-induced agranulocytosis. *Ann Hematol*. 2020;99(11):2477-2482. doi:10.1007/s00277-020-04215-y
- <sup>4</sup> Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med*. 1999 Jan;133(1):15-22. doi: 10.1053/lc.1999.v133.a94931. PMID: 10385477.
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- <sup>6</sup> Dean L. Blood Groups and Red Cell Antigens [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2005. Chapter 9, The Duffy blood group. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK2271/>

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