CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019758Orig1s098

Trade Name:	CLORAZIL
Generic or Proper Name:	(clozapine)
Sponsor:	Heritage Life Science Barbados INC.
Approval Date:	July 29, 2021
Indication:	CLOZARIL is an atypical antipsychotic indicated for: • Treatment-resistant schizophrenia. Efficacy was established in an active controlled study. • Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. Efficacy was established in an active-controlled study.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 019758/ S-98

SUPPLEMENT APPROVAL

Heritage Life Sciences (Barbados) Inc.
c/o HLS Therapeutics USA, Inc.
Attention: Gilbert Godin, Chief Operating Officer
919 Conestoga Road
Building 3, Suite 310
Rosemont, PA 19010

Dear Mr. Godin:

Please refer to your supplemental new drug application (sNDA) dated July 20, 2021, received July 20, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 19758 Clozaril (clozapine HCl) 25 mg and 100 mg Tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Clozapine Risk Evaluation and Mitigation Strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for clozapine products of which Clozaril is a member was originally approved on September 15, 2015, and the most recent REMS modification was approved on February 18, 2021. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS include changes to the frequency of the submission of patient monitoring via a new Patient Status Form and changes to the pharmacy operations to verify safe use conditions for a REMS dispense authorization. In addition, the third part of the goal has been revised from “ensuring compliance with the monitoring schedule for absolute neutrophil count (ANC) prior to dispensing clozapine” to “ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia.” You also proposed additional minor changes to the operation of the REMS program, including certain changes to the audit frequency and information dissemination requirements.

Your proposed modified REMS, submitted to Drug Master File (DMF) 030496 on July 16, 2020, amended and appended to this letter, is approved.

To support continued treatment of patients during the 117 calendar day transition period, the current REMS website, call center, operations, and requirements should remain in effect until the modifications detailed in this letter are fully functional.

- Beginning 26 calendar days after the date of this letter, re-enrollment in the modified REMS for prescribers, patients, pharmacies, and wholesalers-distributors opens.
- The modifications to the approved REMS must be fully functional within 117 calendar days of the date of this letter with the following exceptions:
    - The ANC result provided on the modified Patient Enrollment Form will be valid for 147 calendar days from the date of this letter.
    - Previously enrolled patients who have not re-enrolled in the modified REMS, with a current ANC, can be dispensed clozapine for 207 calendar days from the date of this letter.

The REMS uses a shared system for the elements to assure safe use, an implementation system, and a timetable for assessments of the REMS. This shared system, known as the Clozapine REMS, currently includes products listed on the FDA REMS website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm .

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to every 18 months from the date of this letter.

The REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication

1. **Clozapine REMS Outreach and Communication (18-month assessment post modification approval only)**

    a. The number of professional societies sent the Pharmacy Professional Society Letter or Healthcare Professional Society Letter by date and by method of distribution
        i. Include which professional societies distributed the letter(s) or the content of the letter(s) to their respective members

    b. The number of Pharmacy Letters (by type of pharmacy), Healthcare Provider Letters and Wholesaler-Distributor Letters sent to each stakeholder, respectively, by date(s) and method(s) of distribution. Provide a list of the documents included with each distribution including the revision date

        i. The number and percentage of emailed letters successfully delivered, opened, and unopened

ii. The number and percentage of mailed letters successfully delivered and returned as undeliverable

iii. The number and percentage of faxed letters successfully delivered and returned as undeliverable

c. Date(s) and names of professional meetings where Clozapine REMS materials were disseminated or displayed

d. Report on any communication activities used to inform stakeholders of the modified Clozapine REMS during the transition period of the REMS modification

Program Implementation and Operations

2. REMS Program Implementation and Operations (18-month assessment post-modification only)

a. Date when the modified Clozapine REMS website went live and was fully operational

b. Date when the REMS Contact Center for the modified Clozapine REMS went live and was fully operational

c. Date(s) when healthcare providers could become certified in the modified Clozapine REMS via online or by fax

d. Date(s) when inpatient and outpatient pharmacies could be certified in the modified Clozapine REMS via online or by fax

e. Date when wholesalers-distributors could be authorized in the modified Clozapine REMS via fax

f. Date(s) when patients can be enrolled in the modified Clozapine REMS via website, fax or the REMS Contact Center

g. Stakeholder Transition

i. For each stakeholder category (prescribers, prescriber designees, inpatient pharmacies, outpatient pharmacies, patients, wholesalers/distributors) report:

a) Number transitioned into the modified Clozapine REMS

b) Number certified or enrolled in the REMS program prior to implementation of the modified Clozapine REMS

3. REMS Certification and Enrollment Statistics (provide the two previous, current and cumulative reporting periods beginning with the post-modification 18-month assessment)

a. Healthcare Providers (number and percent)

i. Healthcare Providers who are newly certified

ii. Active prescribers (i.e. who have prescribed clozapine at least once during the reporting period)

iii. Healthcare providers in incomplete status

a) Include a summary of reasons certification is incomplete

iv. For metrics 3.a.i. through iii, stratify by credentials, (e.g. Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other) and geographic region (as defined by US Census)

v. A summary of the methods of prescriber certification (e.g. online, fax)

vi. Prescribers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

b. Prescriber Designees (number and percent)

i. Newly enrolled

ii. Active (associated with active prescriber)

iii. Prescriber designees in incomplete status

a) Include a summary of reasons certification is incomplete

iv. A summary of the methods of prescriber designee certification (e.g. online, fax)

v. Unable to become certified, accompanied by a summary of the reasons they were unable to be certified

c. Patients (number and percent)

i. Newly enrolled

ii. Active patients (i.e. received at least one dispense/authorization of clozapine during the reporting period)

iii. For metrics 3.c.i. and 3.c.ii, stratify by demographics (age, gender, ethnicity, race and geographic region [as defined by US Census]), benign ethnic neutropenia or hospice patient

iv. Of those newly enrolled, the number of unique patients who:

a) Had a yes response on their enrollment form to, Is this patient actively on clozapine therapy?

v. Patient Treatment Status by Patient Type (general population, BEN patients, hospice patients) for the reporting period and cumulatively:

a) Active

b) Interrupted

c) Discontinued

vi. A summary of the methods of patient enrollment (e.g. via online, fax or REMS Contact Center)

vii. Number of patients who were unable to become enrolled (i.e. incomplete status, cancelled), accompanied by a summary of the reasons they were unable to be enrolled

viii. Beginning with the 18-month assessment report: a nationally estimated number of patients that received a dispensed prescription for clozapine (all dosage forms) from U.S. outpatient retail pharmacies for the reporting period. Provide rationale for discrepancies between this estimate and the number of unique patients enrolled in the clozapine REMS and receiving at least one REMS Dispense Authorization during the reporting period.

d. Pharmacies (number and percent)

i. Newly certified in the modified Clozapine REMS

ii. Active pharmacies (i.e. have dispensed clozapine at least once during the reporting period)

iii. Pharmacies in incomplete status

a) Include a summary of reasons certification is incomplete

iv. For metrics 3.d.i. through 3.d.iii, stratify by pharmacy type (inpatient, outpatient) and by geographic region (as defined by US Census)

v. A summary of the methods of pharmacy enrollment (e.g. via online or fax)

vi. Number of pharmacies that were unable to become certified (i.e. incomplete, cancelled), accompanied by a summary of the reasons they were unable to be enrolled

e. Wholesalers-distributors

i. Newly authorized

ii. Active (have shipped clozapine at least once during the reporting period)

4. Clozapine Utilization Data (provide two previous, current and cumulative reporting periods)

a. Number of prescriptions/transactions authorized for dispensing and those dispensed stratified by

i. Prescriber credentials and geographic region

ii. Pharmacy type (inpatient, outpatient)

iii. Patient demographics (age, gender, ethnicity, race, and geographic region [as defined by US Census])

iv. Identify the source of this information

5. REMS Infrastructure and Performance

a. REMS Program Website (provide two previous, current and cumulative reporting periods)

i. Number of visits and unique visits to the REMS website

ii. Number of REMS materials downloaded or printed for each material

iii. A summary of the Clozapine REMS website utilization

The Important Program Update on the Clozapine REMS Website is used to communicate important program changes to stakeholders. This section on the website will provide frequent updates to stakeholders regarding the

program. A summary of the number of updates communicated in this section of the website will be provided during the assessment reporting period.

b. Contact Center Report: (provide current and cumulative reporting periods)

   i. Number of contacts, inbound and outbound, by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesaler/distributors, other)

   ii. A table summarizing the most frequently asked questions (e.g., enrollment question) and by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesaler/distributors, other)

   iii. Summary of reason for contacts (examples may include “Enrollment question,” “Lab query,” etc.) by reporter (authorized representative, pharmacy, healthcare provider, patient/caregiver, wholesaler/distributor).

   iv. If the summary reason for the contact(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues

   v. Reported lack of certified prescribers and/or pharmacies in a patient's local area

   vi. A summary of frequently asked questions (FAQ) by stakeholder type

   vii. Narrative of any corrective actions resulting from issues identified

c. Infrastructure and Performance (provide current and cumulative reporting periods)

   i. Number of times a backup system was used with reasons(s) for each instance (for example, pharmacy level problem, or REMS database problem) clearly defined and described with description of corrective actions taken

   ii. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions

6. REMS Compliance (current reporting period)

a. Audits of inpatient and outpatient pharmacies, wholesalers/distributors, and the REMS program Contact Center will be conducted to ensure that all REMS processes and procedures are in place, functioning, and support the REMS

program, and will be submitted with each assessment report. The audit reports are to include:

i. A copy of the audit plan used for the reporting period

ii. A detailed description of audit findings including the number with no findings, minor, moderate, or serious findings; include information about the root cause of any noncompliance

iii. Number of audited sites in each stakeholder category listed directly above

iv. Number of audits expected, and the number of audits performed

v. Number and types of deficiencies noted for each group of audited stakeholders

vi. Summary of corrective actions taken to address findings, the status of the corrective actions, and any resulting preventative actions that were taken

vii. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time

viii. Documentation of completion of training for relevant staff

ix. The existence of documented processes and procedures for complying with the REMS

x. Verification that at each audited stakeholder's site, the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification

b. For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, if any patient harm resulted, corrective actions taken and any outcome of actions taken. Also provide a summary of non-compliance identified by stakeholder, including but not limited to:

i. For Prescribers, provide: (reported by month for the 18-month assessment only, then per reporting period)
   a) Number of clozapine prescriptions dispensed that were written by non-certified prescribers:

b) Number of unique prescribers that did not submit their patient's ANCs to the REMS program using the *Patient Status Form* on a monthly basis (within 37 calendar days)

c) Number of prescribers that did not submit the patient's ANC results to the REMS program after treatment discontinuation as indicated per the PI

d) Number of healthcare providers that were de-certified and reasons for de-certification. Include if any healthcare providers were re-certified

ii. For Prescriber designees provide:

a) Number of prescriber designees who were non-compliant with the Clozapine REMS requirements

b) Number of prescriber designees that were de-certified and reasons for de-certification

iii. For Patients provide:

a) Number of patients not enrolled in the REMS who were dispensed clozapine

b) Number of patient(s) who received a prescription(s) for clozapine without getting a blood test as ordered by their prescriber and reasons for such if known

iv. For Pharmacies provide:

a) Number and types of pharmacies for which non-compliance with the REMS is detected

b) Number of prescriptions dispensed by noncertified pharmacies stratified by type (inpatient and outpatient) and actions taken to prevent future occurrences (reported or detected through audit)

c) Number of times a clozapine prescription dispensed because a pharmacy bypassed REMS Dispense Authorization; and, if any such events occurred, describe how these events were identified, the root cause of the failure, and any corrective actions taken

d) Number of clozapine prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences

e) Number of times an inpatient pharmacy dispensed more than a 7-days' supply of clozapine to a patient at discharge

f) Inpatient pharmacy dispensing for outpatient use (reported or detected through audit)

g) Number of pharmacies suspended or de-certified by pharmacy type, the reasons for such actions, and actions to address non-compliance

v. For Wholesalers/distributors provide:
   a) The number of authorized wholesalers/distributors for which non-compliance with the REMS is detected

   b) Number of shipments sent to noncertified pharmacies, source of report, and actions taken to prevent future occurrences (reported or detected through audit)

   c) Number of wholesalers/distributors suspended or de-authorized, reasons for such action, and actions to address non-compliance

vi. For REMS Dispense Authorizations (RDA) provide:
   a) Number of REMS Dispense Authorizations (RDA) without current lab value submitted on a *Patient Status Form*, provided as
      1. Total number of unique patients receiving RDA without current lab (i.e., aggregate)
      2. Number of RDAs for each unique patient without current lab; provide mean, median and range of RDAs per patient

   b) Number of RDAs without any ANC (excluding hospice patients) on the submitted *Patient Status Form* and number of these resulting in clozapine dispensing

   c) Number of RDAs without a *Treatment Rationale* provided when the ANC was unacceptable, and number of these resulting in clozapine dispensing

   d) False negatives: e.g., all entities are certified, but system generated a prescription rejection notice

   e) False positives: e.g., one or all entities were not certified but system verified dispensing/generated an RDA

c. For each non-patient stakeholder referred to in section 6.b. above (18-month assessment only)

i. Describe any moderate or serious non-compliance with the REMS that occurred during the first year of transitioning to the modified REMS

ii. Provide an assessment of stakeholder compliance in following the proposed transition plan in transitioning to the modified REMS

d. Number of unique patients receiving a clozapine prescription under a *Dispense Rationale* stratified by type of *Dispense Rationale* and the number of prescriptions authorized under a *Dispense Rationale* per patient in a 6-month timeframe

i. Summary of outreach to prescribers

ii. Summary of resulting prescriber certifications (for non-certified prescriber *Dispense Rationale*)

iii. Summary of resulting *Patient Status Form* submissions (for no monthly *Patient Status Form* submitted)

iv. Number of unique patients who have exceeded or attempted more than the allowable *Dispense Rationales*

e. Number of prescriptions dispensed under a *Dispense Rationale* stratified by prescriber, type of pharmacy and type of *Dispense Rationale*

f. For each reporting period, include a copy of the non-compliance plan used during that reporting period

Safe Use Behaviors

7. Report on Patient Status Forms (PSF) (provide two previous, current and cumulative reporting periods

a. Number of PSFs expected, received, outstanding, and not due as of the cut-off date by the number of active patients

b. Number of PSFs not received within 37 calendar days after the date of the last PSF submission

c. Number of unique patients for whom clozapine treatment was interrupted due to lack of PSF submission or late submission of a PSF

i. Of those patients who resumed therapy after late submission of the PSF, what was the time between when the PSF was due and a successful RDA

ii. Of these patients, the number for whom clozapine was discontinued

d. (For the 18-month, 3-year, and 4½ year assessment reports only) The most common modes of submission of PSFs to the REMS (e.g. fax, online)

e. The number of PSFs where the prescriber responded "no" to the question, "Are you monitoring the patient as recommended in the Prescribing Information (PI)?"

   i. Number of unique patients

   ii. Number of unique prescribers

f. The percentage of unique patients who had their ANCs reported on their PSF in accordance with their monitoring schedule, reported by month (exclude those patients who had a treatment rationale, hospice patients, and patients for whom a dispense rationale was obtained or the prescriber did not submit a PSF for that month)

   i. For those patients on a weekly monitoring schedule ANCs reported:
      a) 0
      b) 1
      c) 2
      d) 3
      e) 4 or more

   ii. For those patients on every two weeks monitoring schedule ANCs reported:
      a) 0
      b) 1
      c) 2 or more

   iii. For those patients on every four weeks monitoring schedule ANCs reported:
      a) 0
      b) 1 or more

8. Report on Prescription Rejections

a. Number of prescriptions submitted for authorization stratified by outcome (authorized or rejected) and authorization type (Clozapine REMS Website or Clozapine REMS Contact Center)

b. Mean, median, and range or the duration of time between rejection and subsequent RDA (for the same patient where both occurred in the reporting period), stratified by authorization type (Clozapine REMS Website or Clozapine REMS Contact Center)

c. Provide reasons for all prescription rejections in the reporting period stratified by type of RDA (via Clozapine REMS Website or Clozapine REMS Contact Center)

    i. Provide mean, median, and range or the duration of time between rejection and subsequent RDA (for the same patient where both occurred in the reporting period), stratified by reasons for prescription rejections

9. Report on *Treatment Rationales*

a. Number of Treatment Rationales submitted
    i. Number per unique patient stratified by patient type (general population, BEN, hospice)

b. Mean, median and range of Treatment Rationales submitted per prescriber

10. Report on Notifications and Alerts

a. Number of notifications and alerts sent, stratified by type and stakeholder type (prescriber, pharmacy) and resulting actions by stakeholder (clozapine discontinued, pharmacy became enrolled, etc.)

    i. For overdue *Patient Status Form* and severe neutropenia notifications, provide the number of notifications per unique patient and any actions by stakeholder (clozapine discontinued, clozapine interrupted, Treatment Rationale submitted, etc.) resulting from the notification.

<u>Evaluation of Knowledge</u>

11. Knowledge Assessments (18-month and 3-year assessments post-modification)

a. Number of completed *Clozapine REMS Knowledge Assessment for Prescribers* and *Clozapine REMS Knowledge Assessment for Pharmacies* (KA) for certified prescribers and pharmacy authorized representatives, and pharmacy staff that have elected to take the KA, including method of enrollment and number of attempts to complete, by stakeholder

b. Summary of the most frequently missed KA questions, stratified by prescriber and pharmacy

c. A summary of potential comprehension or perception issues identified with the KA

d. Proposed remediation for *Clozapine and the Risk of Neutropenia: A Guide for Prescribers, Clozapine and the Risk of Neutropenia: A Guide for Pharmacists*, *Clozapine REMS Knowledge Assessment for Prescribers*, or *Clozapine REMS Knowledge Assessment for Pharmacies.*

12. Periodic Surveys of Prescribers, Pharmacists and Patients (beginning with the 3-Year REMS Assessment Report and thereafter with each assessment report)

A Knowledge, Attitude and Behavior (KAB) Survey will be conducted with random samples of prescribers, pharmacists, and patients who have prescribed, dispensed, or received clozapine.

a. An evaluation of knowledge of certified prescribers of the risk of severe neutropenia, appropriate monitoring of clozapine and REMS requirements

b. An evaluation of knowledge of authorized representatives and pharmacists of the risk of severe neutropenia, appropriate monitoring of clozapine and REMS requirements

c. An evaluation of knowledge of patients or caregivers of the risk of severe neutropenia, and the need for appropriate monitoring

Health Outcomes and/or Surrogates of Health Outcomes

13. Safety Surveillance (per previous two reporting periods, current and cumulatively)

a. Total instances of neutropenia for unique patients stratified by patient type (general population, BEN)
   i. Severe: reported as lowest ANC for each unique patient whose ANC drops below 500/μL within each month
   ii. Moderate: reported as lowest ANC for each unique patient whose ANC drops below 1000/μL, but remains at 500/μL or above within each month
   iii. Mild: reported as lowest ANC for each unique patient whose ANC drops below 1500/μL, but remains at 1000/μL or above within each month

b. For each unique patient identified in a.i (severe neutropenia) provide the time to onset from clozapine initiation to date of lab draw for first ANC consistent with severe neutropenia

c. For each unique patient identified in a.i (severe neutropenia), provide the following stratified by general population patients and BEN patients to include the number and percentage of those with severe neutropenia:

i. After clozapine treatment was interrupted for severe neutropenia, report treatment status on the date of the data cutoff for the reporting period
   a) Treatment was discontinued
   b) Received a treatment rationale
   c) Moved to active status
   d) Remained in interrupted status

ii. Had a daily ANC monitored until ≥1,000 µL general population) or ≥ 500 µL (BEN) as per the PI
   a) Then monitored three times weekly until ANC ≥1,500 µL (general population) or ≥ patient's baseline BEN) as per the PI

iii. Were rechallenged and outcome of the rechallenge (e.g. treatment discontinued, continued on treatment)

iv. Report the mean, median, maximum and minimum number of treatment status changes for unique patients with severe neutropenia

d. Data from the REMS Patient Registry (REMS Data, Postmarketing Adverse Event Data, REMS Contact Center) of known or suspected adverse events due to clozapine-induced neutropenia (e.g. infection) are to be reported regardless of outcome. Provide an overall analysis and discussion of all cases identified from all sources including but not limited to the following for each case: any associated dates, clozapine dosages, dosage changes and ANC values associated with the adverse event.

i. Include all event and prescribing information obtained from the follow-up questions from the REMS Contact Center for each case identified

ii. Number of *Patient Status Forms* that reported a patient had experienced an adverse event due to clozapine-induced neutropenia:
   a) Number and percentage of unique patients

iii. Number of calls made to the REMS Contact Center reporting any adverse event(s) due to clozapine induced neutropenia (e.g. infection)

iv. Include in the analysis prescriber's adherence to baseline and periodic ANC monitoring as described in the PI for each unique case, by case number, in addition to aggregate results

14. Data Sources for Safety Surveillance:

a. Adverse event reports will be processed according to each Applicant's Standard Operation Procedures and criteria outlined in 21 CFR 314.80 The Applicants will process hematologic adverse drug experiences on clozapine collected by the single shared system as follows:

i. All adverse events (hematologic and non-hematologic) will be considered “solicited” events and reported per 21 CFR 314.80(e). In other words, any adverse event collected by the single shared system that is determined to be serious, unexpected, and related will be reported as a 15-Day Alert Report

ii. Individual Case Safety Reports (ICSRs) will be submitted for both serious and non-serious outcomes for all cases of neutropenia (ANC < 1000/µl) for all patients (general population and BEN) per 21 CFR 314.80

iii. Serious, expected events will be reported within the line listing and SOC tabulations in the product’s periodic report

iv. Non-serious neutropenic events (ANC 1000/µl to 1499/µl) not associated with any other adverse event will not be submitted as an Individual Case Safety Report (ICSR). The Clozapine REMS will retain any lab records that fall between 1000/µL and 1499/µL. All ANCs between 1000/µL and 1499/µL will be reported in the REMS Assessment Reports. FDA may request the ICSRs of ANCs that fall within the specified range above, to be provided within a timeline agreed upon with FDA

b. All serious and non-serious adverse events reported for clozapine outside of the single shared system (e.g., an adverse event reported to the sponsor) will be reported in accordance with 21 CFR 314.80

15. **With respect to each goal included in the strategy**, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified (Section 505-1(g)(3)).

16. **Report on Key Performance Indicator:** The key performance indicator (KPI), or the primary metric that will be used to evaluate the success of the Clozapine REMS, is the percentage of patients who received a dispensed prescription for clozapine during the reporting period that had a benefit/risk analysis conducted by the prescriber prior to authorizing clozapine use. Evidence that the benefit/risk analysis has occurred will be fromthe informationsubmitted on the *Patient Enrollment Form* (initial prescription) or the *Patient Status Form* (ongoing prescriptions)

a. Conduct a quarterly analysis of patients prescribed clozapine in the outpatient setting to assess whether a risk/benefit analysis was conducted by the prescriber authorizing clozapine therapy. The threshold for the KPI is as follows:

i. By the last quarter of the 18-month assessment reporting interval prior to data lock, at least 75% of RDAs (excluding those obtained using a dispense rationale or associated with inpatient clozapine use) will be associated with a prescriber having conducted a risk/benefit analysis

ii. Results of each quarterly analysis are to be included in the assessment report

iii. Include a narrative of any process improvement measures or root cause analyses implemented as a result of these quarterly analyses

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rational to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 19758 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 19758 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 19758/S-
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 19758/S-
PRIOR APPROVAL SUPPLEMENT

PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 19758/ S-
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 19758/ S-
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 19758

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ermias Zerislassie, Regulatory Project Manager, at 301-796-2770.

Sincerely,

{See appended electronic signature page}

Marc Stone, M.D.
Deputy Director for Safety
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEAH M HART
07/26/2021 06:39:17 PM

BARBARA A BERGQUIST
07/26/2021 06:44:33 PM

CAROLYN N TIEU on behalf of KATE H OSWELL
07/26/2021 06:53:19 PM

CAROLYN N TIEU
07/26/2021 06:53:47 PM

CYNTHIA L LACIVITA
07/26/2021 08:29:45 PM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC B STONE
07/29/2021 10:21:10 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s098

REMS

RISK EVA A AND MI IGA I S RA EGY (REMS) Document

Clozap ne Shared System REMS Program

I. Adm n strat ve Informat on

Initial Shared System REMS Approval: 09/2015

Most Recent Modification: 07/2021

II. REMS Goal

The goal of the Clozapine REMS Program is to mitigate the risk of severe neutropenia associated with the use of clozapine by:

1. Educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements
2. Informing patients about the risk of severe neutropenia and appropriate monitoring requirements
3. Ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia
4. Ensuring the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the Prescribing Information
5. Establishing long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry

III. REMS Requ rements

Clozap ne Appl cants must ensure that healthcare prov ders, pat ents, pharmac es, and wholesalers-d str butors comply w th the follow ng requ rements:

---

1. Healthcare Prov ders who prescr be clozap ne for outpat ent use and/or n t ate treatment for npat ents must:

To become certified to prescribe

1. Review the drug's Prescribing Information.
2. Review the following: Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers.
3. Successfully complete the Knowledge Assessment for Prescribers and submit it to the REMS Program.
4. Enroll in the REMS Program by completing the Prescriber Enrollment Form.

Before treat t t at o f r t do e)	5. Cou el the pat e t o the r k a oc ated w ith clozap e, clud g evere eutrope a, a d the Clozap e RE Pr Sgra requ re me t clud g to report g of fect o u g A Gu de for Pat e t a d Careg ver : What You M Need to K ow about Clozap e a d Neutrope a. Prov de a copy to the pat e t u le cl cal judg t d cate that the pat e t' adhere ce to the M treat t reg me e w ill be egat vely mp acted by prov d g the Gu de. 6. A e the pat e t' ab olute eutroph l cou t ANC). Docume t a d ub t the ANC to the RE pr Sgra u g the Pat e t E roll t For e 7. E roll the pat e t the RE Pr Sgra by co let g a pd ub tt g the Pat e t E roll t For e to the RE pr Sgram.
Dur g treatme t; accord g to the mo tor g freque cy the Pre cr b g I fo ma t o	8. A e the pat e t' ANC a dmo tor g freque cy. 9. For pat e t w ith a ANC that fall below the acceptable ra ge: A e the pat e t' health tatu for appropr ate e of co t u g treat t. e
Dur g treatme t, thly o	10. Docu t a d ub t the ANC re ult , the tor g fo freque cy, a d appropr ate e for co t u g treatme t to the MS RE progra u g the Pat e t Statu For .
After treatme t M d co t uat o ; M accord g to the mo tor g freque cy the Pre cr b g I for t o a	11. A e the pat e t' ANC. Docume t a d ub t the ANC re ult to the MS RE program u g the Pat e t Statu For .

2. Patients who are prescribed clozapine:

Before treat t t at o	1. Rece ve cou el g fro the pre cr ber of the r k of clozap e a d the ClozapM S RE Progra requ re me t , u g A Gu de for Pat e t a d Careg ver : What You Need to K ow About Clozap e a d Neutrope a. 2. Get a blood te t to check your eutroph l cou t. 3. Be e rolled the MS RE Program. E roll me t fo ma t o w ill be prov ded to the MS RE Progra .
Dur g treatme t; a d rected by your pre cr ber	4. Get a blood te t to check your eutroph l cou t.
After treat t e d co t uat o ; a d rected by your pre cr ber	5. Get a blood te t to check your eutroph l cou t.
At all me M	6. I form the pre cr ber f you have g a d ymp to of fect o .

3. Pharmac ha d p n clozap n for ou pa n u mu :	
To become certi ied to dispense	1. Designate an authorized representative to carry out the certi ication process f and oversee implementation and compliance with the REMS program on behal o the pharmacy. 2. Have the authorized representative review Clozapine and the Risk o Neutropenia: A Guide or Pharmacists. 3. Have the authorized representative success ully complete the Knowledge Assessment or Pharmacies and submit it to the REMS program. 4. Establish processes and procedures to veri y an available, current ANC is f within the acceptable range or patients enrolled but not authorized to receive the drug. 5. Have the authorized representative enroll in the REMS program by completing and submitting the Outpatient Pharmacy Enrollment Form to the REMS program. 6. Train all relevant sta involved in dispensing clozapine on the requirements f o the REMS program using the Clozapine and the Risk o Neutropenia: A Guide or Pharmacists.
Be ore dispensing	. Obtain authorization to dispense each prescription by contacting the REMS Program to veri y that the patient is enrolled and authorized to receive drug. 8. For patients enrolled but not authorized to receive clozapine: Veri y an available, current ANC is within the acceptable range through the processes and procedures established as a requirement o the REMS Program, document and submit the ANC and the prescriber's NPI to the REMS Program and obtain authorization to dispense each prescription by contacting the REMS program to veri y the patient is now authorized to receive clozapine. 9. Report dosing in ormation to the REMS Program.
To maintainf certi ication to f dispense	10. Have the new Authorized Representative enroll in the REMS Program by reviewing Clozapine and the Risk o Neutropenia: A Guide or Pharmacists, f success ully completing the Knowledge Assessment or Pharmacies and the Outpatient Pharmacy Enrollment Form and submitting both to the REMS Program.
At all times f	11. Not distribute, trans er, loan, or sell clozapine except to certi ied dispensers. 12. Maintain records o sta training and that all processes and procedures are in place and are being ollowed. 13. Comply with audits carried out by the manu acturers or a third party acting on behal o the manu acturers, to ensure that all processes and procedures f are in place and are being ollowed.
4. Pharmac ha d p n clozap n for npa n u mu :	

To become cer e o pen e	1. De gna e an au hor ze repre en a ve o carry ou he cer ca on proce an over ee mplemen a on an compl ance w i h he REMS program on behal o he pharmacy. 2. Have he au hor ze repre en a ve rev ew Clozap ne an he R k o Neu ropen a: A Gu e or Pharmac . 3. Have he au hor ze repre en a ve ucce ully comple e he Knowle ge , A e men or Pharmac e an ubmi o he REMS program. 4. E abl h proce e an proce ure o ver y an ava lable curren ANC w i h n he accep able range or pa en enrolle bu no au hor ze o rece ve clozap ne. 5. Have he au hor ze repre en a ve enroll n he REMS program by comple ng an ubmi ng he Inpa en Pharmacy Enrollmen Form o he REMS program. 6. Tra n all relevan a nvolve n pen ng clozap ne on he requ remen o he REMS program u ng he Clozap ne an he R k o Neu ropen a: A Gu e or Pharmac .
Be ore pen ng r o e	7. Ob a n au hor za on o pen e by con ac ng he REMS Program o ver y ha he pa en enrolle an au hor ze o rece ve he rug. 8. For pa en enrolle bu no au hor ze by he REMS Program o rece ve he rug: Ver y an ava lable curren ANC w i h n accep able range hrough he proce e an proce ure e abl he a a requ remen o he REMS Program ocumen an ubmi he ANC o he REMS Program an ob a n au hor za on o pen e each pre cr p on by con ac ng he REMS program o ver y he pa en now au hor ze o rece ve clozap ne.
A charge ,	9. D pen e no more han a 7- ay ' upply.
To ma n a n cer ca on o , pen e	10. Have he new au hor ze repre en a ve enroll n he REMS Program by rev ew ng Clozap ne an he R k o Neu ropen a: A Gu e or Pharmac ucce ully comple ng he Knowle ge A e men or Pharmac e an he Inpa en Pharmacy Enrollmen Form an ubmi ng bo h o he REMS Program.
A all me ,	11. Ma n a n recor o a ra n ng an ha all proce e an proce ure are n place an are be ng ollowe . 12. No r bu e ran er loan or ell clozap ne excep o cer e pen er . 13. Comply w i h au carr e ou by he manu ac urer or a h r par y ac ng , on behal o he manu ac urer o en ure ha all proce e an proce ure are n place an are be ng ollowe .

5. Wholesalers-distributors that distribute clozapine must:

To be able o r bu e	1. E abl h proce e an proce ure o en ure ha he rug r bu e only o cer e pharmac e .

	2. Train a r an aff in o d in di ribu ion on h r quir men of h REMS program.
A a ime c	3. Di ribu on y o r ifi d pharma i . 4.c Main ain r ord of drug di ribu ion for a ozapin hipmen . 5. Main ain r ord ha a pro and pro dur ar in p a and ar b ing fo ow ed. 6. Comp y wi h audi arri d ou by h manufa ur r or a hird par y a ing on b ha f of h manufa ur r , o n ur ha a pro and pro dur ar in p a and ar b ing fo ow ed.

Clozapine Applicants must provide training to healthcare providers who prescribe clozapine.

Th raining in ud h fo owing du a iona ma ria : C ozapin and h Ri k of N eu rop nia: A Guid for H ea h ar Pro id r and h Know l dg A men for Pr rib r . Th raining mu b a ai ab on in and hard opy forma ia mai by a ing h REMS program.

Clozapine Applicants must provide training to pharmacies that dispense clozapine.

Th raining in ud h fo owing du a iona ma ria : C ozapin and h Ri k of N eu rop nia: A Guid for Pharma i and h Know l dg A men for Pharma i . Th raining mu b a ai ab on in and hard opy forma ia mai by a ing h REMS program.

To inform healthcare providers about the REMS Program and the risks and safe use of clozapine, Clozapine Applicants must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials-& Dissemination Plans
Pr rib r r ifi d in h C ozapin REMS c	REMS L r: H a h ar Pro id r L r wi h a a hmen Fa h : Wha ' Chang d in h C ozapin REMS for Pr rib r ? 1. Emai wi hin 30 a ndar day of appro a of h REMS modifi a ion, and again 30 a ndar day a r. a. S nd by mai or fax wi hin 7 a ndar day of h da h ond mai wa n if mai wa r por d und i rab or unop n d.
	2. Emai wi hin 90 a ndar day of appro a of h REMS modifi a ion and again 15 a ndar day a r. a. S nd by mai or fax wi hin 7 a ndar day of h da h ond mai wa n if mai wa r por d und i rab or unop n d.
Pr rib r r ifi d in h C ozapin c REMS wi h 5 or mor pa i n r a d wi h C ozapin	Ou bound Voi Ca : Ca b ginning 30 a ndar day af r appro a of h REMS modifi a ion and mak up o 3 a mp wi hin 90 a ndar day .
Pr rib r no y r - r ifi d in h C ozapin REMS wi h 5 or mor pa i n r a d wi h C ozapin c	Ou bound Voi Ca : 1.c Ca b ginning 120 a ndar day af r appro a of h REMS modifi a ion and mak 1 a mp wi hin 30 a ndar day . 2. Ca b ginning 150 a ndar day af r appro a of h REMS modifi a ion and mak up o 2 a mp wi hin 60 a ndar day .

Target A u e e	Commu o at o Mater als-& D issemi at o Pla s
Healthcare pr viders o wh are likely t prescribe cl zapine	REMS Letter: Healthcare Pr fessi nal S ciety Letter with attachment Factsheet: What's Changed with the Cl zapine REMS Pr gram f r Prescribers?, Dr p In Summary f r Healthcare Pr viders 1. Disseminate within 15 calendar days f appr val f the REMS m dificati n thr ugh the f ll wing pr fessi nal s cieties and request the letter r c ntent be pr vided t their members: a. American S ciety f Hemat l gy, American Psychiatric Ass ciati n American C llege f Psychiatrists, American Ass ciati n f r Geriatric Psychiatry, American Ass ciati n f Chairs f Departments f Psychiatry, American Ass ciati n f Direct rs f Psychiatric Residency o Training, American B ard f Psychiatry and Neur l gy, American C llege f Neur psych pharmac l gy, American Academy f Pediatrics, American Academy f Family Physicians, American Academy f Physicians, American Academy f Physician Assistants, American Academy f Nurse Practiti ners
Auth rized representatives f r inpatient and utpatient pharmacies certified in the Cl zapine REMS	REMS Letter: Pharmacy Letter with attachment Factsheet: What's Changed with the Cl zapine REMS Pr gram f r Pharmacies? 1. Email within 15 calendar days f appr val f the REMS m dificati n and o again 15 calendar days later. a. Send by mail r fax within 7 calendar days f the date the sec nd email was sent if email was rep rted undeliverable r un pened.
Inpatient and utpatient pharmacies likely t dispense cl zapine	REMS Letter: Pharmacy Pr fessi nal S ciety Letter with attachments Factsheet: What's Changed with the Cl zapine REMS Pr gram f r oPharmacies?, Dr p In Summary f r Pharmacies 1. Disseminate, within 15 calendar days f the appr val f the REMS m dificati n, thr ugh the f ll wing pr fessi nal s cieties and request the letter r c ntent be pr vided t their members: a. American Pharmacists Ass ciati n, American S ciety f Health System Pharmacists, Nati nal Ass ciati n f Chain Drug St res, American C llege f Clinical Pharmacy, C llege f Psychiatric and Neur l gic Pharmacists, Nati nal C mmunity Pharmacists Ass ciati n, Nati nal Ass ciati n f Specialty Pharmacies, Pharmaceutical Care Management Ass ciati n
Wh lesalers-distribut rs enr lled in the Cl zapine o REMS	REMS Letter: Wh lesaler-Distribut r Letter with attachment Factsheet: What's Changed with the Cl zapine REMS Pr gram f r Pharmacies? 1. Email within 30 calendar days f appr val f the REMS m dificati n and again 15 calendar days later. a. Send by mail r fax within 7 calendar days f the date the sec nd email was sent if email was rep rted undeliverable r un pened. 2. Request the Factsheet be pr vided ne time t all pharmacies rdering cl zapine between August 21, 2021 and December 31, 2021.
Healthcare pr viders o	Website P p-Up Message 1 1. Publish pr minently n www.cl zapinerems.c m within 7 calendar days f the appr val f the REMS m dificati n and display f r 109 calendar days. The Message must appear the first time a stakeh lder l gs int the o system f ll wing launch f the message and require an active click t cl se it.

Target Au e e	Commu g at o Mater als-& D issemi at o Pla s
	Important Pro ram Update 1. Publish prominently at www.clozapinerems.com within 7 calendar days of the approval of the REMS modification and display for 109 calendar days.
	Website Pop-Up Messa e 2 1. Publish prominently on the public homepa e at www.clozapinerems.com on November 15, 2021 and display for 90 calendar days. The Messa e must appear with each visit to the homepa e and require an active click to close it.

To s pport REMS program operat o s, Clozap e Appl a ts must:

1. Authorize dispensin for each patient based on verifyin the patient is enrolled, and receipt of the g Patient Status Form on the followin schedule:
   Authorize the first dispensin based on receipt of the Patient Enrollment Form.

   For subsequent dispensin s, the Patient Status Form must be received within 37 calendar days after the date of the last Patient Status Form. If the Patient Status Form is not received within 37 calendar days, the patient is not authorized to receive the dru until a completed form is received g or a current ANC (result obtained within the last 30 calendar days) within the acceptable ran e is provided to a pharmacist up to three times per patient per year for outpatient dispensin s.

2. Establish and maintain the REMS pro ram website,www.clozapinerems.com. The REMS pro ram website must include the capability to: complete prescriber and pharmacy certification online, enroll and mana e patients online includin ANC results and patient authorization status; and print the Prescribin Information, Medication Guide, and REMS materials. All product websites for healthcare providers and consumers must include prominent REMS-specific links to the REMS pro ram website. g The REMS pro ram website must not link back to the promotional product websites.

3. Make the REMS Pro ram website fully operational and all REMS materials available throu h the website and coordinatin center within 117 calendar days of the REMS modification (November 15, 2021).

4. Establish and maintain a REMS Pro ram coordinatin center for REMS participants at 888-586-0758.

5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the Clozapine REMS Pro ram.
6. Ensure that prescribers and pharmacies are able to become certified by fax and online.

7. Ensug e prescribers are able to enroll patients by fax and online.

8. Ensure prescribers are able to report ANC results by phone, fax usin the Patient Status Form, and online.

9. Ensure pharmacies are able to report ANC results by phone, fax usin the ANC Lab Reportin Form and online.

10. Ensure prescribers are able to authorize continuin clozapine treatment for patients when the prescriber determines the benefits outwei h the risks of developin severe neutropenia by fax, phone, and online.

11. Ensure pharmacies are able to enroll as inpatient (for purposes of this REMS, includin but not limited to a pharmacy dispensin clozapine only to patients receivin inpatient medical care and other related services for sur ery, acute medical conditions, or injuries (usually for a short-term illness or condition)) g or outpatient (for purposes of this REMS, includin but not limited to retail dru stores,

ambulator ar harma i s, and harma i s dis nsing to long-t rm ar , r habilitation fa iliti s, and rison s st ms).

12. Ensur harma i s ar abl to obtain authorization to dis ns b hon and onlin .

13. Provid loza in and th Risk of N eutro nia: A Guid for H alth ar Provid rs to H alth ar Provid rs who (1) Att mpt to r s rib loza in and ar not t rtifi d, or (2) Inquir about how to C b ome rtifi d.

14. Provid loza in and th Risk of N eutro nia: A Guid for Pharma ists to harma ists who (1) Att mpt to dis ns loza in and ar not t rtifi d, or (2) Inquir about how to b om rtifi d.

15. Notif r s rib rs and harma i s within 24 hours aft r th b ome rtifi d in th REMS rogram.

16. Pr6vid rtifi d r s rib rs6a ss to th databas of rtifi d harma i s and nroll d ati nts.

17. Pr6vid rtifi d harma i s a ss to th databas of rtifi d r s rib rs and nroll d ati nts.

18. Provid authoriz d whol sal rs-distributors a ss to th databas of rtifi d harma i s.

19. Establish and maintain a r gistr whi h in lud s a r orting and oll tion s st m for all ati nts to rovid information on s v r n utro nia.

20. Ensur that on a r ort of s v r n utro nia r sulting in hos italization or d ath is r iv d, loza in A li ants follow u with th h alth ar rovid r to obtain all r quir d data for th r gistr .

To ensure REMS participants' compliance with the REMS program, Clozapine Applicants must:

21. Ensur th Pati nt Status Form is r iv d for a h ati nt nroll d in th REMS Program: If th form is not r iv d within 31 al ndar da s of th dat of th last Pati nt Status Form, loza in A li ants must onta t th r s rib r for th form.

22. Maintain ad quat r ords to d monstrat that th REMS r quir ments hav b n met, in luding, but limit d to r ords of: loza in distribution and dis nsing; rtifi ation of r s rib rs, and harma i s, and authorization of whol sal rs-distributors; nroll d ati nts; and audits of REMS arti i ants. Th s r ords must b r adil availabl for FDA ins tions.

23. Establish a lan for addr ssing non omplian with REMS Program r quir ments.

24. Monitor r s rib rs, harma i s, and whol sal rs-distributors on an ongoing basis to nsur th r quir ments of th loza in REMS Program ar b ing met. Tak orr tiv a tion if non omplian is id ntifi d, in luding d - rtifi ation.

25. V rif v r two ars that th d signat d authoriz d r r s ntativ for th harma is th same. If diff r nt, th harma must r - rtif with a n w authoriz d r r s ntativ .

26. Audit annuall 10% of rtifi d out ati nt harma i s (maximum 400) and 10% of rtifi d in ati nt harma i s (maximum 400) that hav ord r d loza in in th r vious 12 months to nsur that all C ro ss s and ro dur s ar in la , fun tioning, and su ort th REMS Program r quir ments.

27. Audit whol sal r-distributors no lat r than 180 al ndar da s aft r th whol sal r-distributor is authoriz d and annuall th r aft r to nsur that all ro ss s and ro dur s ar in la , fun tioning, and su ort th REMS Program r quir ments. Th annual audit must in lud all whol sal rs-distributors that distribut d loza in in th r vious 12 months.

28. Tak r asonabl st s to improv impl mentation of and omplian with th r quir ments of th C loza in REMS Program bas d on monitoring and valuation of th loza in REMS Program.

IV. REMS c t Ti tabl

Clozapine NDA Appli ants must submit REMS Assessments 18 months from the date of the approval of the July 29, 2021 modifi ation and every 18 months thereafter. To fa ilitate in lusion of as mu h information as possible while allowing reasonable time to prepare the submission, the reporting interval overed by ea h assessment should on lude no earlier than 60 alendar days before the submission date for that assessment. Clozapine NDA Appli ants must submit ea h assessment so that it will be re eived by the FDA on or before the due date.

V. REMS Mat rial

The following materials are part of the Clozapine REMS**:** c

E roll t For

Pres riber:

1. Pres riber Enrollment Form

Patient:

2. Patient Enrollment Form

Pharma y:

3. Outpatient Pharma y Enrollment Form
4. Inpatient Pharma y Enrollment Form

Trai i g a d Educatio al Mat rial

Pres riber:

5. Clozapine and the Risk of Neutropenia: A Guide for Health are Providers
6. Knowledge Assessment for Pres ribers

Patient:

7. A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia

Pharma y:

8. Clozapine and the Risk of Neutropenia: A Guide for Pharma ists c
9. Knowledge Assessment for Pharma ies

Pati t Car For

10. Patient Status Form
11. ANC Lab Reporting Form

Co icatio Mat rial u

12. Health are Provider Letter
13. Health are Professional So iety Letter
14. Drop In Summary for Health are Providers
15. Pharma y Letter
16. Pharma y Professional So iety Letter
17. Drop In Summary for Pharma ies
18. Wholesaler-Distributor Letter
19. Fa tsheet: What's Changed with the Clozapine REMS Program for Pres ribers
20. Fa tsheet: What’s Changed with the Clozapine REMS Program for Pharma ies c
21. Website Pop-Up Message 1
22. Website Pop-Up Message 2
23. Important Program Update c

Other Mater a

. REMS program website (www. lozapineREMS.com) C

CLOZAPINE REMS

Prescriber Enrollment Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Prescribers who prescribe clozapine only to patients receiving inpatient medical care and other related services for surgery, acute medical conditions or injuries (usually for a short-term illness or condition) are not required to be certified in the Clozapine REMS. Patients in this setting are required to be enrolled in the Clozapine REMS in order to receive clozapine.

For immediate certification, please go to www.clozapinerems.com.

Instructions

Clozapine is only available through the Clozapine REMS (Risk Evaluation and Mitigation Strategy). In order to become certified and prescribe clozapine, you must:

1. Review the Prescribing Information for clozapine and *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
2. Successfully complete and submit the *Clozapine REMS Knowledge Assessment for Prescribers*
3. Complete and submit this one-time *Clozapine REMS Prescriber Enrollment Form*

Prescriber Responsibilities

I have:

- Reviewed the drug's Prescribing Information for clozapine.
- Reviewed the **Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers**.
- Successfully completed the **Knowledge Assessment for Prescribers** and submitted it to the Clozapine REMS.

Before treatment initiation (first dose), I must:

- Counsel the patient or caregiver on the risks associated with clozapine, including severe neutropenia, and the Clozapine REMS requirements including to report signs of infection using **A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia.**
- Provide a copy of the Guide to the patient unless clinical judgment indicates that the patient's adherence to the treatment regimen will be negatively impacted by providing the Guide.
- Assess the patient's absolute neutrophil count (ANC). Document and submit the ANC to the Clozapine REMS using the **Patient Enrollment Form**.
- Enroll the patient in the Clozapine REMS by completing and submitting the **Patient Enrollment Form** to the Clozapine REMS.

During treatment; according to the monitoring frequency in the Prescribing Information, I must

- Assess the patient's ANC and monitoring frequency.
- For patients with an ANC that falls below the acceptable range: Assess the patient's health status for appropriateness of continuing treatment.

During treatment, monthly, I must:

- Document and submit the ANC results, the monitoring frequency, and appropriateness for continuing treatment to the Clozapine REMS using the **Patient Status Form.**

After treatment discontinuation; according to the monitoring frequency in the Prescribing Information, I must:

- Assess the patient's ANC. Document and submit the ANC results to the REMS program using the **Patient Status Form**.

I understand that if I do not maintain compliance with the requirements of the Clozapine REMS, I will no longer be able to prescribe Clozapine.

I understand that personnel from the Clozapine REMS or a designated third party acting on behalf of the Clozapine Sponsors may contact me to gather information, resolve discrepancies, or to provide other information related to the Clozapine REMS.

I understand that clozapine manufacturers or their agents and contractors may contact me via phone, mail or email to survey me on the effectiveness of the program requirements for the Clozapine REMS.

Continued on the next page

CLOZAPINE REMS

Prescriber Information (All Fields Required Unless Otherwise Indicated)		
First Name:	MI (opt):	Last Name:
Individual NPI #:		Individual DEA #:
Email Address:		
Credentials: ☐ MD ☐ NP ☐ PA ☐ DO ☐ Other		
Clinic/Practice Name:		
Address:		
City:	State:	Zip Code:
Phone:	Ext (opt):	Fax (opt.):
Preferred Time of Contact (opt.): ☐ Morning ☐ Afternoon ☐ Evening		
Preferred Method of Contact (opt.): ☐ Text to Mobile # ☐ Email ☐ Phone Call		

Prescriber's Signature:_____ **Date (MM/DD/YYYY):**_____

Submit this form:

- Online at www.clozapinerems.com
- Via fax to 1-800-878-5927

You will receive a confirmation via email

CLOZAPINE REMS

Patient Enrollment Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Instructions for Prescribers and Prescriber Designees

This form may be completed by a certified prescriber or a prescriber designee.

Complete this form for a patient if:

- re-enrolling a patient into the Clozapine REMS
- the patient has never been treated with clozapine previously, or
- you have never treated this patient with clozapine (regardless of the patient's history of clozapine treatment)

A prescriber must complete the form to designate the patient as a Benign Ethnic Neutropenia (BEN) patient or a Hospice Care patient. A prescriber designee may not complete the form for these patients.

For immediate enrollment, please go to www.clozapinerems.com.

For enrollment via fax, please complete all required fields below and fax to 800-878-5927. For enrollment via the Clozapine REMS Contact Center, please call 888-586-0758. Enrollment confirmation will be sent via the contact preference specified on the prescriber's *Clozapine REMS Prescriber Enrollment Form*.

Clozapine is only available through the single shared Clozapine REMS (Risk Evaluation and Mitigation Strategy). In order to treat a patient with clozapine, the patient MUST be enrolled in the Clozapine REMS. To enroll a patient, you must:

1. Inform the patient or caregiver about the risk of severe neutropenia with clozapine and the Clozapine REMS requirements including to report signs of infection
2. Provide the patient or caregiver with *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia* unless you determine that the patient's adherence to the treatment regimen will be negatively impacted by providing the *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia* and informing them about this risk
3. Complete and submit this *Clozapine REMS Patient Enrollment Form*

Patient Information (* Required Field)

First Name*:	Last Name*:
Gender*: ☐ Male ☐ Female ☐ Other	Date of Birth* (MM/DD/YYYY): / /
Race*: ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Caucasian ☐ Native Hawaiian or Other Pacific Islander ☐ Other: _____	
Ethnicity*: ☐ Hispanic or Latino ☐ Not Hispanic or Latino	
Phone:	Email Address:
Does the patient have a permanent address*? ☐ Yes ☐ No	Zip Code:

Patient Status (* Required Field)

Is this patient actively on clozapine therapy*? ☐ Yes ☐ No ☐ Unknown

If Yes, what is this patient's current monitoring frequency?

☐ 3 times a week ☐ Every 2 weeks ☐ Weekly ☐ Monthly

Baseline or Most Recent Lab Information (All Fields Required)

Blood Draw Date (MM/DD/YYYY):	ANC (per µL):

Continued on next page

Prescriber Information (* Required Field)		
First Name*:	Last Name*:	Individual NPI Number*:
Phone:	Email:	Fax:

Prescriber Designee Information (All Fields Required if Form is Completed by a Prescriber Designee)		
First Name*:	Last Name*:	
Phone*:	Fax:	Email:

Benign Ethnic Neutropenia (BEN) Patient Attestation (Prescriber signature required for attestation of BEN diagnosis)

A BEN patient designation provides a separate ANC monitoring algorithm for the patient. The BEN designation is a permanent status.

By signing below, I attest that the above is a patient with documented benign ethnic neutropenia.

Prescriber Signature: _____ **Date (MM/DD/YYYY):** _____

Hospice Care Patient Attestation (Prescriber signature required for attestation of 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 frequency of submitting a Patient Status Form to once every 6 months after a discussion with the patient and his/her caregiver. To change the frequency of submitting a Patient Status Form to once every 6 months for a hospice patient, the prescriber must sign below:

By signing below, I attest that the above is a hospice care patient.

Prescriber Signature: _____ **Date (MM/DD/YYYY):** _____

CLOZAPINE REMS

Outpatient Pharmacy Enrollment Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Complete this form if your pharmacy 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.

For immediate certification, please go to www.clozapinerems.com.

Instructions

Use this form to enroll a SINGLE pharmacy location. To enroll MULTIPLE pharmacy locations, you must go to www.clozapinerems.com.

Clozapine is only available through the Clozapine REMS (Risk Evaluation and Mitigation Strategy). In order to dispense clozapine, the pharmacy must designate an authorized representative.

The authorized representative for the pharmacy must:

1. Review *Clozapine and the Risk of Neutropenia: A Guide for Pharmacists.*
2. Successfully complete and submit the *Knowledge Assessment for Pharmacies.*
3. Complete and submit this *Outpatient Pharmacy Enrollment.*

Authorized Representative Responsibilities

As the Authorized Representative, I must:

- Review **Clozapine and the Risk of Neutropenia: A Guide for Pharmacist.**
- Successfully complete **the Knowledge Assessment for Pharmacies** and submit it to the Clozapine REMS.
- Establish processes and procedures to verify an available, current ANC is within the acceptable range for patients enrolled but not authorized to receive the drug.
- Train all relevant staff involved in dispensing clozapine on the requirements of the Clozapine REMS using the **Clozapine and the Risk of Neutropenia: A Guide for Pharmacists**.

Before dispensing, all pharmacy staff must:

- Obtain authorization to dispense each prescription by contacting the Clozapine REMS to verify that the patient is enrolled and authorized to receive 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 to verify the patient is now authorized to receive clozapine.
- Report dosing information to the Clozapine REMS.

All pharmacy staff must

- Not distribute, transfer, loan, or sell clozapine except to certified dispensers.
- Maintain records of staff training and that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers, to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, any new Authorized Representative must:

- Enroll in the Clozapine REMS by reviewing **Clozapine and the Risk of Neutropenia: A Guide for Pharmacists,** successfully complete the **Knowledge Assessment for Pharmacies** and the **Outpatient Pharmacy Enrollment Form** and submit both to the Clozapine REMS.

Continued on Page 2

CLOZAPINE REMS

Outpatient Pharmacy Enrollment Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Outpatient Pharmacy Information (All Fields Required Unless Otherwise Indicated)

Pharmacy Name:			Organization NPI #:
Address:			DEA # (opt.)
City:		State:	Zip Code:
Phone:	Ext (opt):	Fax (opt.):	

The name, location, and phone number of your pharmacy will be publicly available on ClozapineREMS.com. If you do not want your information available, please call the Clozapine REMS Contact Center at 1-888-586-0758.

Allow this pharmacy to be found on the Clozapine REMS website as a: ☐ Retail Pharmacy ☐ Specialty Pharmacy

Authorized Representative Information (All Fields Required Unless Otherwise Indicated)

First Name:	Last Name:	Position/Title:
Email Address:		
Credentials: ☐ RPh ☐ PharmD ☐ BCPS ☐ Other		
Phone:	Ext (opt):	Fax (opt.):
Preferred Method of Contact (opt.): ☐ Text to Mobile # ☐ Email ☐ Phone Call		

Authorized Representative's Signature:_____

Date (MM/DD/YYYY):_____

Submit this form:

- Online at www.clozapinerems.com
- Via fax to 1-800-878-5927

You will receive a confirmation via email

CLOZAPINE REMS

Inpatient Pharmacy Enrollment Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Complete this form if your pharmacy is 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).

If your pharmacy 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, please complete the Clozapine REMS Outpatient Pharmacy Enrollment Form.

For immediate certification, please go to www.clozapinerems.com.

Instructions

Use this form to enroll a SINGLE pharmacy location. To enroll MULTIPLE pharmacy locations, you must go to www.clozapinerems.com.

Clozapine is only available through the Clozapine REMS (Risk Evaluation and Mitigation Strategy). In order to dispense clozapine, the pharmacy must designate an authorized representative.

The authorized representative for the pharmacy must:

1. Review *Clozapine and the Risk of Neutropenia: A Guide for Pharmacists.*
2. Successfully complete and submit the *Knowledge Assessment for Pharmacies.*
3. Complete and submit this *Inpatient Pharmacy Enrollment Form.*

Authorized Representative Responsibilities

As the Authorized Representative, I must:

- Review **Clozapine and the Risk of Neutropenia: A Guide for Pharmacists.**
- Successfully complete the **Knowledge Assessment for Pharmacies** and submit it to the Clozapine REMS.
- Establish processes and procedures to verify an available, current ANC is within the acceptable range for patients enrolled but not authorized to receive clozapine.
- Train all relevant staff involved in dispensing clozapine on the requirements of the Clozapine REMS, using the **Clozapine and the Risk of Neutropenia: A Guide for Pharmacists**.

Before first dose, all pharmacy staff must:

- Obtain authorization to dispense by contacting the Clozapine REMS to verify that the patient is enrolled and 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 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.

At discharge, all pharmacy staff must:

- Dispense no more than a 7-days' supply.

At all times, all pharmacy staff must:

- Maintain records of staff training and that all processes and procedures are in place and are being followed.
- Not distribute, transfer, loan, or sell clozapine except to certified dispensers.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers, to ensure that all processes and procedures are in place and are being followed.

To maintain certification to dispense, any new Authorized Representative must:

- Enroll in the Clozapine REMS by reviewing **Clozapine and the Risk of Neutropenia: A Guide for Pharmacists,** successfully complete the **Knowledge Assessment for Pharmacies** and the **Inpatient Pharmacy Enrollment Form** and submit both to the Clozapine REMS.

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CLOZAPINE REMS

Inpatient Pharmacy Enrollment Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Inpatient Pharmacy Information (All Fields Required Unless Otherwise Indicated)			
Pharmacy Name:			Organization NPI #:
Address:			DEA # (opt.)
City:		State:	Zip Code:
Phone:	Ext (opt):	Fax (opt.):	

Authorized Representative Information (All Fields Required Unless Otherwise Indicated)		
First Name:	Last Name:	Position/Title:
Email Address:		
Credentials: ☐ RPh ☐ PharmD ☐ BCPS ☐ Other		
Phone:	Ext (opt):	Fax (opt.):
Preferred Method of Contact (opt.): ☐ Text to Mobile # ☐ Email ☐ Phone Call		
Authorized Representative's Signature:_____		**Date (MM/DD/YYYY):**_____

Submit this form:

- Online at www.clozapinerems.com
- Via fax to 1-800-878-5927

You will receive a confirmation via email

CLOZAPINE REMS

Clozapine and the Risk of Neutropenia:

A Guide for Healthcare Providers

This Guide discusses:

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

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

CLOZAPINE REMS

Table of Contents

1 The Clozapine REMS

Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/µL). 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 and document each clozapine patient's ANCs to the Clozapine REMS monthly, by submitting the Patient Status 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

Inpatient Pharmacies

- Must certify in the Clozapine REMS to dispense clozapine

  Must obtain a REMS Dispense Authorization (RDA) before the **initial** dispensing of 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 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

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**

*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/µL
- "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 ANCs 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/µL for the general population
- at least 1000/µL 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 ANCs.

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/µL for the general population, ANC greater than or equal to 1000/µL 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 ≥ 1500/µL	• Initiate treatment • If treatment interrupted: - < 30 days, continue monitoring as before • - ≥ 30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	• 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/µL)*	• Continue treatment	• Three times weekly until ANC ≥ 1500/µL • Once ANC ≥ 1500/µL, return to patient's last "Normal Range" ANC monitoring interval**
Moderate Neutropenia (500 - 999/µL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Resume treatment once ANC normalizes to ≥ 1000/µL	• Daily until ANC ≥ 1000/µL, then: • Three times weekly until ANC ≥ 1500/µL • Once ANC ≥ 1500/µL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**
Severe Neutropenia (< 500/µL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥ 1000/µL • Three times weekly until ANC ≥ 1500/µL • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1500/µL

* Confirm all initial reports of ANC less than 1500/µL 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 ≥1000/μL)	• Obtain at least two baseline ANC levels before initiating treatment • If treatment interrupted: - < 30 days, continue monitoring as before - ≥ 30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	• 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)*	• Recommend hematology consultation • Continue treatment	• Three times weekly until ANC ≥ 1000/μL or ≥ patient's known baseline. • Once ANC ≥ 1000/μL 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)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥ 500/μL • Three times weekly until ANC ≥ patients baseline • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/μL 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

Moderate Neutropenia (500 to 999/μL)*	**GENERAL POPULATION** • Daily until ANC ≥ 1000/μL, then • Three times weekly until ANC ≥ 1500/μL
Severe Neutropenia (less than 500/μL)*	**GENERAL POPULATION** • Daily until ANC ≥ 1000/μL, then • Three times weekly until ANC ≥ 1500/μL
	BEN POPULATION • Daily until ANC ≥ 500/μL • Three times weekly until ANC ≥ patients established baseline

* Confirm all initial reports of ANC less than 1500/μL (ANC < 1000/μL 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/μL) or severe clozapine-related neutropenia (ANC less than 500/μL), 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

New

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:

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

New

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/µL (general population) or less than 500/µL (patients with BEN)?

When a patient's ANC is less than 1000/µL (general population) or less than 500/µL (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/μL for the general population) or severe neutropenia (ANC < 500/μL 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.

CLOZAPINE REMS

Knowledge Assessment for Prescribers

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Instructions

1. Complete Section 1 below to ensure the Knowledge Assessment is associated with your program record.
2. Answer all questions in Section 2.
3. Fax the completed *Knowledge Assessment for Prescribers* to the Clozapine REMS at **800-878-5927**.

For real-time processing of this Knowledge Assessment, please go to www.clozapinerems.com.

1 Prescriber Information (PLEASE TYPE OR PRINT)

First Name:	**MI (opt):**	**Last Name:**
Individual NPI #:	**Individual DEA #:**	
Email Address:		
Clinic/Practice Name:		
Address:		
City:	**State:**	**Zip Code:**
Phone:	**Ext. (opt):**	**Fax (opt.):**

2 Knowledge Assessment

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 single shared Clozapine REMS.

A. True
B. False

Question 2

Clozapine is associated with severe neutropenia, which can lead to serious infection and death.

A. True
B. False

Question 3

Severe neutropenia is defined as:

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

Question 4

Before initiating treatment with clozapine:

A. A baseline absolute neutrophil count (ANC) must be at least 1000/µL for a patient with documented benign ethnic neutropenia (BEN)
B. A baseline absolute neutrophil count (ANC) must be at least 1500/µL for a patient who is part of the general population (i.e., the patient does not have documented BEN)
C. A baseline absolute neutrophil count (ANC) is not necessary
D. Both A and B

Continued on next page

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Question 5

Before clozapine treatment initiation, a certified prescriber must:

A. Determine if the patient has documented BEN
B. Enroll the patient in the Clozapine REMS
C. Counsel the patient/caregiver about the risk of severe neutropenia
D. Order blood work to obtain an ANC
E. Review the ANC and submit it to the Clozapine REMS
F. All of the above

Question 6

In the outpatient setting, prescribers must submit the *Patient Status Form* monthly, to the single shared Clozapine REMS, *before* the patient can be dispensed clozapine.

A. True
B. False

Question 7

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 8

Regarding patients with documented BEN, which of the following statements are true?

A. Patients with BEN have a different clozapine treatment algorithm and monitoring requirements
B. Patients 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

Continued on next page

Question 9

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 10

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 ≥ 1500/µL if the patient is part of the general population (i.e., if the patient does not have documented BEN)

B. Mild neutropenia is within the normal range for a patient with documented BEN

C. If the patient has documented 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 11

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 documented BEN

B. If the patient is part of the general population (i.e., if the patient does not have documented BEN), interrupt therapy and conduct ANC monitoring: daily until ANC ≥ 1000/µL; three times weekly until ANC ≥ 1500/µL; 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 12

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 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 documented BEN), interrupt treatment and conduct ANC monitoring: daily until ANC ≥ 1000/µL; three times weekly until ANC ≥ 1500/µL

C. The patient may still be rechallenged with clozapine at the discretion of the prescriber

D. All of the above

Required for all prescribers	**Prescriber Signature** **X**	**Date:** / /

CLOZAPINE REMS

A Guide for Patients and Caregivers:

What You Need to Know about Clozapine and Neutropenia

Patients:

- Review this Guide with your doctor, pharmacist, or nurse.
- Ask questions!
- Make sure you understand what you need to do to receive Clozapine.

What is clozapine?

Clozapine is a prescription medicine to treat people with schizophrenia who have not responded to other medicines. Clozapine may also reduce the risk of suicidal behavior.

What is the most serious risk of clozapine treatment?

Clozapine can cause a blood condition (severe neutropenia), which can lead to serious infections and death. Neutropenia occurs when you have too few of a certain type of white blood cells called neutrophils. This makes it harder for your body to fight infections.

Why do I need to have blood tests?

Getting your blood tested is important because a low number of neutrophils may not cause any symptoms until you have an infection. Having a blood test helps your doctor know if you are more likely to get an infection.

You must have regular blood tests before you start taking clozapine and during your treatment. This test is called absolute neutrophil count (ANC). If the number of neutrophils, or ANC, is too low, you may have to stop clozapine. Your doctor will decide if or when it is safe to restart clozapine.

What are the symptoms of infection?

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

If you have any of these symptoms, talk to your doctor right away

What can I do to help reduce the risk of developing neutropenia?

Three important things you can do:

1. Have your blood tested as instructed by your doctor.
2. Tell your doctor about all the medicines you are taking (prescription and over-the-counter) and if you start a new medicine.
3. Tell your doctor right away if you get a fever, feel sick, or have any signs of infections.

What are the blood testing requirements for clozapine?

Get your Blood Tested	• Your doctor will give you an order to have blood tests done. • You will need to get your blood tested on the following schedule or as directed by your doctor: - Weekly blood tests for the first 6 months you are taking clozapine - Every 2 weeks for the next 6 months if your ANC stays normal - Monthly after the first year if your ANC stays normal
Results	• If your ANC is too low, your doctor will schedule blood tests more frequently.
Stay on Clozapine	• The Clozapine REMS will keep track of your blood test results so your doctor and pharmacist know if it is safe to fill your clozapine prescription.

How do I receive my clozapine from the pharmacy?

Only certain pharmacies are allowed to provide you with clozapine. Your doctor will help you find a pharmacy.

Remember: You must get your blood tested before you can receive clozapine from your pharmacy!

What is the Clozapine Risk Evaluation and Mitigation Strategy (REMS)?

A REMS is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medicines with serious safety concerns. Drug companies and healthcare providers must take extra steps to make sure the benefits of using the drug are more than the risks. Clozapine has a REMS because treatment with clozapine may cause a blood condition (severe neutropenia), which can lead to serious infections and death.

Where can I get more information about clozapine?

If you would like more information, talk to your doctor or visit www.clozapinerems.com.

Report any side effects directly to the Clozapine REMS at **888-586-0758**.
You can also report negative side effects to the FDA at www.fda.gov/medwatch, or call **800-FDA-1088**.

CLOZAPINE REMS

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

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

Table of Contents

1 The Clozapine REMS

Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/µL). 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

New

  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

New

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

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

*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/µL
- "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 ANCs 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/μL for the general population
- at least 1000/μL 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 ANCs.

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/μL for the general population, ANC greater than or equal to 1000/μL 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 ≥ 1500/µL	• Initiate treatment • If treatment interrupted: - < 30 days, continue monitoring as before • - ≥ 30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	• 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/µL)*	• Continue treatment	• Three times weekly until ANC ≥ 1500/µL • Once ANC ≥ 1500/µL, return to patient's last "Normal Range" ANC monitoring interval**
Moderate Neutropenia (500 - 999/µL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Resume treatment once ANC normalizes to ≥ 1000/µL	• Daily until ANC ≥ 1000/µL, then: • Three times weekly until ANC ≥ 1500/µL • Once ANC ≥ 1500/µL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**
Severe Neutropenia (< 500/µL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥ 1000/µL • Three times weekly until ANC ≥ 1500/µL • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1500/µL

* Confirm all initial reports of ANC less than 1500/µL 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 ≥1000/μL)	• Obtain at least two baseline ANC levels before initiating treatment • If treatment interrupted: - < 30 days, continue monitoring as before - ≥ 30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	• 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)*	• Recommend hematology consultation • Continue treatment	• Three times weekly until ANC ≥ 1000/μL or ≥ patient's known baseline. • Once ANC ≥ 1000/μL 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)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥ 500/μL • Three times weekly until ANC ≥ patients baseline • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/μL 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/µL, 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/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 3** as shown below.

Table 3 Recommended monitoring frequency when clozapine treatment is discontinued

Moderate Neutropenia (500 to 999/μL)*	**GENERAL POPULATION** • Daily until ANC ≥ 1000/μL, then • Three times weekly until ANC ≥ 1500/μL
Severe Neutropenia (less than 500/μL)*	**GENERAL POPULATION** • Daily until ANC ≥ 1000/μL, then • Three times weekly until ANC ≥ 1500/μL
	BEN POPULATION • Daily until ANC ≥ 500/μL • Three times weekly until ANC ≥ patients established baseline

* Confirm all initial reports of ANC less than 1500/μL (ANC < 1000/μL 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/μL) or severe clozapine-related neutropenia (ANC less than 500/μL), 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*
- Sucessfully 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 discontinue

Obtain an RDA in one of two ways:

New

- 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 discontinue

New

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.

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 and 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 discontinue

New

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.

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 ANCs 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 and 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/μL for the general population) or severe neutropenia (ANC < 500/μL 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.

CLOZAPINE REMS

Knowledge Assessment for Pharmacies

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Instructions

1. Complete Sections 1 and 2 below to ensure the Knowledge Assessment is associated with your program record.
2. Answer all questions in Section 3.
3. Fax the completed *Knowledge Assessment for Pharmacies* to the Clozapine REMS at **800-878-5927**.

For real-time processing of this Knowledge Assessment, please go to www.clozapinerems.com.

1 Pharmacy Information (PLEASE TYPE OR PRINT)

Pharmacy Name:		**Organization NPI #:**	
Address:			
City:		**State:**	**Zip Code:**
Phone:	**Ext. (opt):**	**Fax (opt.):**	

2 Pharmacy Authorized Representative Information

First Name:	**MI (opt):**	**Last Name:**
Email Address:		
Phone:	**Ext. (opt):**	**Fax (opt.):**

3 Knowledge Assessment

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 single shared Clozapine REMS.

A. True
B. False

Question 2

Clozapine is associated with severe neutropenia, which can lead to serious infection and death.

A. True
B. False

Question 3

Severe neutropenia is defined as:

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

Continued on next page

Question 4

Before initiating treatment with clozapine:

A. A baseline absolute neutrophil count (ANC) must be at least 1000/μL for a patient with documented benign ethnic neutropenia (BEN)

B. A baseline absolute neutrophil count (ANC) must be at least 1500/μL for a patient who is part of the general population (i.e., the patient does not have documented BEN)

C. A baseline absolute neutrophil count (ANC) is not necessary

D. Both A and B

Question 5

Before clozapine treatment initiation, a certified prescriber must:

A. Determine if the patient has documented BEN

B. Enroll the patient in the Clozapine REMS

C. Counsel the patient/caregiver about the risk of severe neutropenia

D. Order blood work to obtain an ANC

E. Review the ANC and submit it to the Clozapine REMS

F. All of the above

Question 6

Prescribers must submit the *Patient Status Form* monthly, to the Clozapine REMS, *before* the patient is authorized to be dispensed clozapine.

A. True

B. False

Question 7

Before each outpatient dispensing or before the first inpatient dispensing for a patient, the pharmacist must:

A. Verify the patient is enrolled in the Clozapine REMS

B. Verify the patient is authorized to receive drug

C. Obtain a REMS Dispense Authorization each time from the REMS

D. For patients enrolled but not authorized by the Clozapine REMS to receive clozapine, document and submit an available, current ANC that is within acceptable range and obtain a Dispense Rationale

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

Continued on next page

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Fax: 800-878-5927
www.clozapinerems.com

Question 9

Regarding patients with documented BEN, which of the following statements are true?

A. Patients with BEN have a different clozapine treatment algorithm and monitoring requirements

B. Patients 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

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 ≥ 1500/μL if the patient is part of the general population (i.e., if the patient does not have documented BEN)

B. Mild neutropenia is within the normal range for a patient with documented BEN

C. If the patient has documented 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 documented BEN

B. If the patient is part of the general population (i.e., if the patient does not have documented BEN), interrupt therapy and conduct ANC monitoring: daily until ANC ≥ 1000/μL; three times weekly until ANC ≥ 1500/μL; 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

Continued on next page

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

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 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 documented BEN), interrupt treatment and conduct ANC monitoring: daily until ANC ≥ 1000/µL; three times weekly until ANC ≥ 1500/µL

C. The patient may still be rechallenged with clozapine at the discretion of the prescriber

D. All of the above

Required	**Signature**	**Date:**
	X	/ /

CLOZAPINE REMS

Patient Status Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Instructions

Assess the patient by obtaining complete blood counts, including the absolute neutrophil count (ANC), as described in the Prescribing Information. Record the ANC data on this form.

You can complete this form online at www.clozapinerems.com or fax it to the Clozapine REMS Contact Center at 1-800-878-5927.

This form must be completed monthly for each patient continuing treatment with clozapine. Please submit page 1 and any pages that apply to your patient's monitoring frequency.

This form may also be used to:

- **Interrupt, Discontinue, or Resume Treatment**
- **Designate the patient as a Benign Ethnic Neutropenia patient**
- **Create a Treatment Rationale when the patient's ANC level is < 1000/µL for a general population patient or < 500/µL for a BEN patient**
- **Designate the patient as a Hospice patient**

This form can be used by both a prescriber and prescriber designee. The following activities require the signature of a certified prescribe:

- **Designating a patient as a Hospice Care patient**
- **Designating a patient as a Benign Ethnic Neutropenia patient**
- **Authorizing the continuation of therapy if one or more required labs are missing**
- **Creating a Treatment Rationale for a patient**

By submitting this form, you are authorizing this patient to continue treatment on clozapine, unless Interrupt Treatment or Discontinue Treatment is selected.

Prescriber Information (* Indicates a Required Field)

First Name*:	Last Name*:	Individual NPI #*:
Phone*:	Email Address*:	Fax:

Prescriber Designee Information (* Indicates a Required Field if form is completed by a Prescriber Designee)

First Name*:	Last Name*:	
Phone*:	Email Address*:	Fax*:

Patient Information (* Indicates a Required Field)

First Name*:	Last Name*:	REMS Patient ID:
Date of Birth*: MM / DD / YYYY	Zip Code:	Gender: ☐ Male ☐ Female ☐ Other

Patient Status (* Indicates a Required Field)

1. Are you monitoring the patient as recommended in the Prescribing Information?* ☐ **Yes** ☐ **No**

2. What is the patient's current monitoring frequency?* ☐ **3 times a week** ☐ **Every 2 weeks** ☐ **Weekly** ☐ **Monthly**

3. Change the patient's monitoring frequency to*: ☐ **3 times a week** ☐ **Every 2 weeks** ☐ **No Change to the Monitoring Frequency** ☐ **Weekly** ☐ **Monthly**

4. Did the patient experience any adverse event(s) due to clozapine-induced neutropenia (e.g. infection)?*
   ☐ **No**
   ☐ **Yes** → **If yes, please provide a phone number where you may be reached by the Clozapine REMS Contact Center for additional information related to this event: (_____) _____-_____.**

Hospice Care patient designation. This section must be completed by the prescriber. The prescriber must sign below.

*For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the **prescriber** may reduce the frequency of submitting a Patient Status Form to once every 6 months after a discussion with the patient and his/her caregiver.* To change the frequency of submitting a Patient Status Form to once every 6 months for a hospice patient, **the prescriber must sign below.**

By signing below, I attest that the above is a hospice care patient.

Prescriber Signature: **Date** (MM/DD/YYYY):

Benign Ethnic Neutropenia (BEN) patient designation. This section must be completed by the prescriber. The prescriber must sign below.

A BEN patient designation provides a separate ANC monitoring algorithm for the patient. The BEN designation is a permanent status.

By signing below, I attest that the above is a patient with documented benign ethnic neutropenia.

Prescriber Signature: **Date** (MM/DD/YYYY):

Continue to the next pages to provide ANC Lab Data

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Reporting ANC Lab Data

Instructions for entering ANC lab data on the following pages:

1. **Locate the section below that aligns with the patient's current monitoring frequency**
2. **Enter the blood draw date and the ANC range in the appropriate patient population (general or BEN) column or enter the ANC value.**
3. **If a lab is missing, select the reason for missing the lab. Note: If one or more labs are missing, the prescriber is required to authorize the continuation of therapy by providing a signature and date.**
4. **Report of an ANC lab value indicating moderate (general population) or severe neutropenia (general or BEN population) requires treatment to be interrupted or discontinued or the creation of a Treatment Rationale by the prescriber unless a more recent ANC lab value is provided that is ≥ 1000/μL for a general population patient or ≥ 500/μL for a BEN population patient.**

Weekly Monitoring Frequency (Enter data for the last four weekly blood draws for this patient)

Blood Draw Date	General Patient Population	BEN Patient Population		ANC (per μL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	☐ Normal Range (≥ 1500/μL) ☐ Mild Neutropenia (1000 to 1499/μL) ☐ Moderate Neutropenia (500 to 999/μL) [2] ☐ Severe Neutropenia (< 500/μL) [2]	☐ Normal BEN Range (≥ 1000/μL) ☐ BEN Neutropenia (500 to 999/μL) ☐ BEN Severe Neutropenia (< 500/μL) [2]	or	ANC (per μL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/μL) ☐ Mild Neutropenia (1000 to 1499/μL) ☐ Moderate Neutropenia (500 to 999/μL) [2] ☐ Severe Neutropenia (< 500/μL) [2]	☐ Normal BEN Range (≥ 1000/μL) ☐ BEN Neutropenia (500 to 999/μL) ☐ BEN Severe Neutropenia (< 500/μL) [2]	or	ANC (per μL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/μL) ☐ Mild Neutropenia (1000 to 1499/μL) ☐ Moderate Neutropenia (500 to 999/μL) [2] ☐ Severe Neutropenia (< 500/μL) [2]	☐ Normal BEN Range (≥ 1000/μL) ☐ BEN Neutropenia (500 to 999/μL) ☐ BEN Severe Neutropenia (< 500/μL) [2]	or	ANC (per μL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/μL) ☐ Mild Neutropenia (1000 to 1499/μL) ☐ Moderate Neutropenia (500 to 999/μL) [2] ☐ Severe Neutropenia (< 500/μL) [2]	☐ Normal BEN Range (≥ 1000/μL) ☐ BEN Neutropenia (500 to 999/μL) ☐ BEN Severe Neutropenia (< 500/μL) [2]	or	ANC (per μL):

[1] Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.
[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: **Date** (MM/DD/YYYY):

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) (Prescriber Signature required below)

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/μL for the general population) ***or*** *severe neutropenia (ANC<500/μL for general population and patients with benign ethnic neutropenia). check* **and sign below**:

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.

Until (MM/DD/YYYY) __________________ (not to exceed 6 months)

Prescriber Signature: **Date** (MM/DD/YYYY):

Continue to the next page for additional monitoring frequencies

Every 2 Weeks Monitoring Frequency (Enter data for the last two every two weeks blood draws for this patient)

Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	General Patient Population	BEN Patient Population	or	ANC (per µL):
	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]		

Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	General Patient Population	BEN Patient Population	or	ANC (per µL):
	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]		

[1] Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.
[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: **Date** (MM/DD/YYYY):

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) **(Prescriber Signature required below)**

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) ***or*** *severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia).* check **and sign below**:

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.

Until (MM/DD/YYYY) _____ (not to exceed 6 months)

Prescriber Signature: **Date** (MM/DD/YYYY):

Monthly Monitoring Frequency (Enter data for the last monthly blood draw for this patient)

Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	General Patient Population	BEN Patient Population	or	ANC (per µL):
	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]		

[1] Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.
[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: **Date** (MM/DD/YYYY):

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) **(Prescriber Signature required below)**

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) ***or*** *severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia).* check **and sign below**:

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.

Until (MM/DD/YYYY) _____ (not to exceed 6 months)

Prescriber Signature: **Date** (MM/DD/YYYY):

Continue to the next page for additional monitoring frequencies

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

3 Times Weekly Monitoring Frequency (Enter all ANC lab data collected in the last four weeks).
This section may also be used to record ANCs for patients requiring daily monitoring.

	General Patient Population	**BEN Patient Population**		ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	

Continued on next page

CLOZAPINE REMS

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Patient Status Form

Blood Draw Date:	General Patient Population	BEN Patient Population		ANC (per µL):
MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	**General Patient Population** ☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	**BEN Patient Population** ☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	**General Patient Population** ☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	**BEN Patient Population** ☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	**General Patient Population** ☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	**BEN Patient Population** ☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab**[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	**General Patient Population** ☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) [2] ☐ Severe Neutropenia (< 500/µL) [2]	**BEN Patient Population** ☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL) [2]	or	ANC (per µL):

[1] **Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.**

[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: **Date** (MM/DD/YYYY):

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) (Prescriber Signature required below)

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) ***or*** *severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia).* check **and sign below**:

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.

Until (MM/DD/YYYY) __________________ (not to exceed 6 months)

Prescriber Signature: **Date** (MM/DD/YYYY):

CLOZAPINE REMS

ANC Lab Reporting Form

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Fax: 800-878-5927
www.clozapinerems.com

For immediate online reporting of an ANC Lab, please go to www.clozapinerems.com.

1. **This form may be used by:**
   a. **certified prescribers and their designees to submit an ANC Lab outside of the monthly reporting requirement (using the Patient Status Form), and**
   b. **certified pharmacies to submit an ANC Lab.**

2. A reported ANC Lab that is < 1000/µL for a general population patient or < 500/µL for a BEN patient will cause the patient's treatment to be interrupted until:

- **The patient's prescriber determines that the benefits of continuing clozapine outweigh the risk of neutropenia; or**
- **A more recent ANC lab value is provided that is ≥ 1000/µL for a general population patient or ≥ 500/µL for a BEN population patient**

3. **Submission of an ANC Lab Reporting Form is not a substitute for the prescriber's requirement to document and submit ANC results, the monitoring frequency, and appropriateness for continuing treatment monthly using the monthly Patient Status Form.**

Patient Information (* Indicates a Required Field)

First Name*:	Last Name*:	Date of Birth*: MM / DD / YYYY
REMS Patient ID:	Zip Code:	Gender: ☐ Male ☐ Female ☐ Other

Reporter Information (* Indicates a Required Field)

First Name*:	Last Name*:	Phone*:

Prescriber's Individual NPI #*: **or** Pharmacy's Organizational NPI #*:

ANC Lab (Lab draw date required, enter either a range or the ANC for General Population or BEN Population)

Blood Draw Date:	General Patient Population	BEN Patient Population		ANC (per µL):
MM / DD / YYYY	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL) ☐ Severe Neutropenia (< 500/µL)	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)	or	

TO:

SUBJECT: FDA Required Changes to the Clozapine REMS; Prescriber Re-certification Required

PREVIEW TEXT: Re-certify and Re-enroll Patients Now

CLOZAPINE REMS

Re-certify and Re-enroll Patients Now

Dear Healthcare Provider,

The Clozapine REMS requirements are changing due to a recently approved modification. New Clozapine Requirements will be implemented **November 15, 2021.** Prescribers and patients who are not re-certified or re-enrolled after this time will not have access to clozapine.

- **Re-certify in the Clozapine REMS** in order to prescribe clozapine for outpatient use and/or initiate treatment for inpatients.
- **Re-enroll patients** continuing on clozapine treatment to avoid a break in patient treatment.
- **Re-certification of prescribers and their designees, and re-enrollment of patients must be done with the revised materials.** To do this, you may access the new clozapine REMS website **beginning August 16, 2021:**
    - Go to www.clozapinerems.com.
    - Click on the link in the **Important Program Update**. You will be taken to the modified Clozapine REMS website.
    - Prescribers must create new login credentials.
    - Click on Log-in | Register tab. These credentials will only work on the modified Clozapine REMS.
    - Prescribers must first review the Prescriber Training, complete and submit the Knowledge Assessment and Prescriber Enrollment Form to become re-certified
    - Then re-enroll your patients using the Patient Enrollment Form.
- A **Transition Contact Center** is available at 888-586-0758 to support re-certification, re-enrollment activities and to answer questions.
- After launch of the modified clozapine REMS on November 15, 2021, a **NEW Patient Status Form** must be submitted monthly. The Patient Status Form documents the patient's ANC results, monitoring frequency, and appropriateness to continue treatment.
    - Continue monitoring **existing patients** according to their current monitoring schedule using the ANC Lab Reporting Form prior to November 15, 2021. All existing patients will need to be re-enrolled in the new program by November 15, 2021.

- All **new patients starting clozapine** between now and November 15, 2021 must be enrolled in both the current program and the new program.

- See Fact Sheet: What's Changed in the Clozapine REMS for Prescribers for more details on these and other changes to the program.

Re-certify and re-enroll your patients prior to November 15th to avoid delays in patient treatment!

Questions? Contact the Clozapine REMS Transition Call Center at **1-888-586-0758.**

TO: [Professional Society]

SUBJECT: Request to share important Clozapine REMS changes with members

PREVIEW TEXT: Changes in Requirements, Re-certification Needed in Clozapine REMS

CLOZAPINE REMS

Dear Professional Society,

A modification to Clozapine REMS has been recently approved and will be launched in November 15, 2021. We are asking for your help in sharing this important information with your members as there are significant changes to the requirements of the program.

- Prescribers must **re-certify** in the new Clozapine REMS in order to prescribe clozapine for outpatient use and/or initiate treatment for inpatients after November 15, 2021.
- **Prescribers and Prescriber Designees can start re-certifying on August 16, 2021.**
- Prescribers and Prescriber Designees must also **re-enroll patients** continuing on clozapine treatment. Patients can be re-enrolled starting **August 16, 2021.**

We have included a Drop In Summary (attached) of information to help with disseminating the important changes to the clozapine REMS, actions that prescribers must take to continue to provide clozapine treatment, and where to go to find more information.

We have also included a Fact Sheet: What's Changed in the Clozapine REMS for Prescribers for more details on these and other changes to the program.

Please encourage your members to re-certify and re-enroll their patients prior to Nov 15th to avoid delays in patient treatment!

We thank you for your assistance.

Sincerely,

Clozapine REMS

Drop in Summary – Prescriber

Clozapine REMS Changes are Coming in November

O November 15, 2021, the Cloz pi e REMS will impleme t ch ges to the progr m requireme ts.

Prescriber Re-Certification and Patient Re-enrollment Required

- Prescribers will ee to **re-certify** i the Cloz pi e REMS **re-enroll their patients** to co ti ue to prescribe cloz pi e for outp tie t use /or i iti te tre tme t for i p tie ts fter November 15, 2021.
- Prescriber esig ees must lso re-e roll. Prescriber esig ees m a re-e roll p tie ts.
- To re-certif , prescribers must re the revise tr i i g, successfull complete the k owle ge ssessme t complete ew e rollme t form.
    - **Go to the current www.clozapineREMS.com and look for Important Program Update or pop-up message with information and link to revised Clozapine REMS platform.**
    - O l the revise prescriber p tie t e rollme t forms will be ccepte .
    - A Tr sitio Co t ct Ce ter is v il ble t 888-586-0758 to support re-certific tio , re-e rollme t ctivities to swer questio s.

REMS Requirement Changes

- Begi i g November 15, 2021, ew P tie t St tus Form will ow ocume t p tie t mo itori g for ll outp tie ts. Although p tie t mo itori g must co ti ue per the Prescribi g I form atio , the reporti g o the P tie t St tus Form must be submitte mo thl . The P tie t St tus Form ocume ts the p tie t's ANC results, mo itori g freque c , ppropri te ess to co ti ue tre tme t.
    - Co ti ue to mo itor **existing patients** ccor i g to the curre t REMS requireme ts prior to the November 15, 2021 l u ch of the ew Cloz pi e REMS Progr m. All existi g p tie ts will ee to be re-e rolle i the ew progr m b November 15, 2021.
    - All **new patients starting clozapine** betwee ow November 15, 2021, must be e rolle i both the curre t progr m the ew progr m.

- A ew Cloz pi e REMS website pl tform will be v il ble to mo itor tr ck p tie ts with perso lize o li e shbo r . This ew website pl tform lso h s ll the ew m ateri ls prescribers will ee to re-certif re-e roll p tie ts is v il ble t the ew cloz pi e REMS website.
- A f ctsheet title "Wh t's Ch ge i the Cloz pi e REMS for Prescribers?" expl i s the iffere ces from the curre t mo ifie Cloz pi e REMS progr m.

Key Dates: !

- **August 2, 2021-** The ew co t ct ce ter will be v il ble to swer questio s for st kehol ers t 1-888-586-0758.
- **August 16, 2021-** All re-certific tio re-e rollme t for ll st kehol ers begi s.
- **November 15, 2021-** New cloz pi e REMS is l u che . !

Re-certif re-e roll our p tie ts prior to **November 15th** to voi el s i p tie t tre tme t !

TO: [for email version only]

SUBJECT: FDA Required Changes to the Clozapine REMS: Pharmacy Re-certification Required [for email version only]

PREVIEW TEXT: "Switch" system removal from Clozapine REMS; Re-certification needed [for email version only)

CLOZAPINE REMS

Switch System will be removed November 15, 2021; Re-certification required

Dear Authorized Representative,

The Clozapine REMS requirements are changing due to a recently approved modification. New Clozapine requirements will be implemented on November 15, 2021.

Starting November 15, 2021

- The current "switch" pharmacy management system is being removed. A REMS dispense authorization will only be provided by accessing either the modified Clozapine REMS website platform or the Clozapine REMS Call Center by phone.
- Only pharmacies with Authorized Representatives re-certified in the Clozapine REMS will be able to dispense clozapine.
- New processes and procedures may need to be put in place for your pharmacy to be able to continue dispensing clozapine.

Authorized Representatives must **re-certify** for your pharmacy to continue to dispense clozapine. You may re-certify beginning August 16, 2021. In order for an individual pharmacist to re-enroll in the Clozapine REMS, the certified Authorized Representative will need to invite the pharmacist to enroll in the program using a valid email address.

- Large chain pharmacies may call the Clozapine REMS Contact Center at 1-888-586-0758 to arrange for a bulk upload of stores and staff.

Starting August 16, 2021

- **Re-certification will open August 16th at the new Clozapine REMS Website.** To reach this new clozapine REMS website:
  - Go to www.clozapinerems.com.
  - Click on the link in the **Important Program Update**. You will be taken to the new Clozapine REMS website.
  - Authorized Representatives must create new log-in credentials.

- Click on **Log-in | Register** tab. These credentials will only work on the modified Clozapine REMS website.
- Authorized Representatives must first review the Pharmacy Training, complete and submit the Knowledge Assessment and Pharmacy Enrollment Form to become re-certified.

- Additionally, the Clozapine REMS Transition Call Center will be available on August 2, 2021 to help guide you through the re-certification process at 1-888-586-0758.
- Authorized Representatives must also train pharmacy staff using new materials and send staff an invitation to re-enroll after they are trained.
- See Fact Sheet: What's Changed in the Clozapine REMS for Pharmacies for more details on these and other changes to the program.

Re-certify prior to November 15th to avoid delays in patient treatment!

Questions?

The Clozapine REMS Transition Call Center at **1-888-586-0758** can answer any questions you may have beginning August 2nd.

Signed,

CPMG

TO: [Professional Society]

SUBJECT: Request to share important Clozapine REMS changes with members

PREVIEW TEXT: "Switch" system removal from Clozapine REMS; Re-certification needed [for email version only)

CLOZAPINE REMS

Dear Professional Society,

A modification to the Clozapine REMS has been recently approved and will be launched on November 15, 2021. We are asking for your help in sharing this important information with your members as there are significant changes to the program.

The "switch" system is being removed as a way to verify clozapine dispensing. Pharmacists will now need to go to www.clozapineREMS.com or call the Clozapine REMS Contact Center to verify information and obtain a REMS dispense authorization to dispense clozapine.
New processes and procedures may need to be put in place for pharmacies to be able to continue to dispense clozapine.

Pharmacy Authorized Representatives will also need to re-certify in the Clozapine REMS.

We have included a Drop In Summary (attached) of information to help with disseminating the important changes to the Clozapine REMS, actions that pharmacies must take to continue to dispense clozapine, and where to go to find more information.

We have also included a Fact Sheet: What's Changed in the Clozapine REMS for Pharmacies for more details on these and other changes to the program.

Please encourage your members to re-certify prior to Nov 15th to avoid delays in patient treatment!

We thank you for your assistance.

Sincerely,

Clozapine REMS

Drop in S r Ph r c

Cloz pine REMS Ch nges esi re Co ng nb Nove er

Ph r mc S ste Ch nges

- O November 15, 2021, a ew Clozapi e REMS will be lau ched with cha ges to the program requireme ts.
  - Begi i g November 15, 2021, the curre t "switch" system or pharmacy ma ageme t system that is curre tly used as a optio to verify a dispe se authorizatio will be removed. New processes a d procedures may eed to be put i place for your pharmacy to be able to co ti ue dispe si g clozapi e.
  - Pharmacists will eed to go to www.clozapi eREMS.com or call the Clozapi e Call Ce ter to verify i formatio a d obtai a REMS dispe se authorizatio to dispe se clozapi e.
  - A factsheet titled "What's Cha ged i the Clozapi e REMS For Pharmacies?" explai s the differe ces from the curre t a d modified Clozapi e REMS program a d is available at the ew clozapi e REMS website.

A thorized Represent tive Re certific tion Req ired

- Pharmacy Authorized Represe tatives will eed to re-certify i the ew Clozapi e REMS for the pharmacy to be able to dispe se clozapi e.
- Authorized Represe tatives must also trai pharmacy staff with the ew trai i g materials.
- All pharmacists who will be obtai i g a REMS dispe se authorizatio will eed to be e rolled or n re-e rolled i order to dispe se clozapi e.
- A ew clozapi e REMS website platform will be available to track patie ts with a pharmacy dashboard.
- To re-certify, Authorized Represe tatives must read the revised trai i g, successfully complete n the k owledge assessme t a d complete a ew e rollme t form.
  - **Go to c rrent www.cloz pineREMS.co nd look for l orp mn Progr Upd te or pop p ss ge with infor tion nd link to revised Cloz pine REMS pl tfor .**
  - O ly the revised pharmacy e rollme t forms will be accepted.
  - The Clozapi e REMS Tra sitio Call Ce ter will be available o August 2, 2021 to help guide you through the re-certificatio process at 1-888-586-0758.
  - Large chai pharmacies may call the Clozapi e REMS Co tact Ce ter at 1-888-586-0758 to arra ge for a bulk upload of stores a d staff.

Ke D tes:

- **A g st 16, 2021** Authorized Represe tatives ca begi to re-certify.
- **m b Nove er 15, 2021** New clozapi e REMS is lau ched.

Re-certify prior to **Nove er 15th** to avoid delays i patie t treatme t! n

<Date>

ACT ON NEEDED: Changes to the Clozapine REMS

Subject: - Current wholesalers/distributors must re-enroll in the Clozapine REMS
- Program changes effective (DATE).
- Request assistance with informing pharmacies of changes

Dear Wholesaler/Distributor:

The Clozapine REMS requirements and REMS Administrator are changing. As a result, you will need to take action and re-enroll in order to continue distributing clozapine.

Starting November 15, 2021, you may only distribute clozapine when:

1. You re-enroll in the modified Clozapine REMS as a distributor through the Clozapine REMS,
2. The requesting pharmacy is certified in the modified Clozapine REMS, and
3. You verify the pharmacy's certification through the Clozapine REMS.

Please complete and return the enclosed Wholesaler-Distributor Registration Form by faxing it to 800-878-5927 by November 15, 2021 to ensure you may continue to distribute in the modified Clozapine REMS. Once your re-enrollment is complete, you will be contacted to coordinate receiving the new daily pharmacy eligibility file.

In addition, the Clozapine REMS Sponsors request your assistance in preparing pharmacies for the modified Clozapine REMS. Between the dates of August 15, 2021 and December 31, 2021, please provide copies of the enclosed Pharmacy Letter and Fact Sheet: What's Changed with the Clozapine REMS Program for Pharmacies to any pharmacy that orders clozapine.

For additional information related to the Clozapine REMS and recent program modifications, please call **1-888-586-0758**.

Sincerely,

Clozapine REMS

CLOZAPINE REMS

What's Changed in the Clozapine REMS for Prescribers?

Phone: 888-586-0758
Fax: 800-878-5927
ww.clozapinerems.com

Starting November 15, 2021, requirements to the Clozapine REMS will change.

What are the important changes for prescribers and their designees?

During Treatment

Previous Requirement	New Requirement
Using the *ANC Lab Reporting Form*, submit ANC according to the patient's monitoring frequency on file with the Clozapine REMS as described in the Monitoring Schedule of the Prescribing Information. • For weekly monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 7 days of the lab draw* date. • For every two weeks monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 15 days of the lab draw* date. • For monthly monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 31 days of the lab draw* date.	**Monthly**, using the new *Patient Status Form*, document the patient's ANC results, the monitoring frequency, and appropriateness for continuing treatment and submit to the Clozapine REMS. The prescriber must authorize the continuation of therapy if one or more ANC is missing for the month. Individual ANCs may still be submitted when obtained by completing and submitting an *ANC Lab Reporting Form*.

After Treatment Discontinuation

Previous Requirement	New Requirement
	Assess the patient's ANC according to the monitoring frequency in the Prescribing Information. Document and submit the ANC results to the Clozapine REMS using the *Patient Status Form*.

CLOZAPINE REMS

More Information about the New Patient Status Form

This form must be completed monthly for each patient continuing treatment with clozapine. This form may also be used to:

- Interrupt, Discontinue, or Resume Treatment
- Designate the patient as a Benign Ethnic Neutropenia patient
- Create a Treatment Rationale when the patient's ANC level is < 1000/μL for a general population patient or < 500/μL for a BEN patient
- Designate the patient as a Hospice patient

The *Patient Status Form* may be completed by a certified prescriber or their designee. However, the following actions require the signature of a certified prescriber on the *Patient Status Form*:

- Designating a patient as a Hospice Care patient
- Designating a patient as a Benign Ethnic Neutropenia patient
- Authorizing the continuation of therapy if one or more required labs are missing
- Creating a Treatment Rationale for a patient

A *Patient Status Form* must be received withing 37 calendar days after the date of the *Patient Enrollment Form* or the last *Patient Status Form*.

If the *Patient Status Form* is not received within 37 calendar days, the patient is not authorized to receive clozapine until a completed form is received. If the *Patient Status Form* is missing, the pharmacist, if in possession of a current ANC within the acceptable range, may use a Dispense Rationale to dispense clozapine to the patient. A Dispense Rationale may be used up to three times per patient per year for outpatient dispensing.

The following questions are required to be answered on the *Patient Status Form*:

Are you monitoring the patient as recommended in the Prescribing Information? Yes/No

What is the patient's current monitoring frequency? 3 times weekly, Weekly, Every 2 weeks, Monthly

Did the patient experience any adverse event(s) due to clozapine-induced neutropenia (e.g., infection)? Yes/No

The Patient Status Form may be submitted online or via a fax.

- To submit online, log into your account at www.clozapinerems.com and select the Manage Patient button. Select the Create or Add buttons for the appropriate patient.
- To submit via fax, complete the form and fax to 800-878-5927.

CLOZAPINE REMS

How to Submit ANCs using the ANC Lab Reporting Form

ANCs may still be submitted via the *ANC Lab Reporting Form* online or via fax.

- To submit online, log into your account at www.clozapinerems.com and select the Manage Patient button. Select the Create or Add buttons in the Patient Status Form (PSF) column for the appropriate patient.
- To submit via fax, complete the ANC Lab Reporting Form and fax to 800-878-5927.

The Patient Status Form must still be submitted monthly.

CLOZAPINE REMS

What's Changed in the Clozapine REMS for Pharmacies?

Phone: 888-586-0758
Fax: 800-878-5927
ww.clozapinerems.com

Starting November 15, 2021, requirements to the Clozapine REMS will change.

What are the important changes for pharmacies?

Obtaining Authorization to Dispense for Outpatient Pharmacies

Previous Requirement	New Requirement
Obtain a **Predispense Authorization (PDA)** each time from the Clozapine REMS by accessing the Clozapine REMS website, Clozapine REMS Contact Center, or enabling the SWITCH (pharmacy management system) to support communication with the Clozapine REMS.	Obtain a **REMS Dispense Authorization (RDA)** to dispense each prescription **ONLY** by accessing the Clozapine REMS website or the Clozapine REMS Contact Center to verify that the patient is enrolled and authorized to receive the drug. **RDAs may no longer be obtained via the SWITCH (the pharmacy management system).**

A REMS Dispense Authorization (RDA) Verifies…

The patient is enrolled by a certified prescriber or prescriber designee.

A Patient Status Form has been completed by a certified prescriber or prescriber designee in the last 37 days.

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

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

For a subsequent dispensing, the RDA will verify that:

- 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

If a Patient Status Form is not received, the pharmacist may use a Dispense Rationale to dispense (see Dispense Rationale below).

CLOZAPINE REMS

Dispense Rationale	
Previous Requirement	**New Requirement**
To avoid disruption in patient care, and to allow certified outpatient pharmacies an opportunity to apply clinical judgment to continue to dispense clozapine to enrolled patients, certified outpatient pharmacies will be allowed to provide a "Dispense Rationale" when a patient's **prescriber is not certified** in the Clozapine REMS.	To avoid disruption in patient care, and to allow certified outpatient and inpatient pharmacies an opportunity to apply clinical judgment to continue to dispense clozapine to enrolled patients, certified pharmacies will be allowed to provide a "Dispense Rationale" when a ***Patient Status Form* is not received** from the patient's prescriber within 37 days of the patient's enrollment or previous *Patient Status Form*. The Dispense Rationale will be automatically presented to the pharmacist when the RDA is rejected for this reason. To provide a Dispense Rationale, the pharmacist must be in possession of: - A current ANC (within 30 days of the attempted fill) within an acceptable range for the patient - The prescriber's NPI number Three Dispense Rationales may be used per patient per year by outpatient pharmacies. There is no limit to the number of Dispense Rationales used by inpatient pharmacies.

Information about the New Patient Status Form

This form must be completed monthly by a certified prescriber or their designee for each patient continuing treatment with clozapine.

This form may also be used to:

- Interrupt, Discontinue, or Resume Treatment
- Designate the patient as a Benign Ethnic Neutropenia patient
- Create a Treatment Rationale when the patient's ANC level is < 1000/µL for a general population patient or < 500/µL for a BEN patient
- Designate the patient as a Hospice patient

A *Patient Status Form* must be received withing 37 calendar days after the date of the *Patient Enrollment Form* or the last *Patient Status Form*.

The certified prescriber or their designee must provide the ANCs according to the patient's current monitoring frequency. If an ANC is missing, the prescriber is required to provide authorization to continue therapy.

Continued on next page

CLOZAPINE REMS

Information about the New Patient Status Form (continued)
The *Patient Status Form* may also be used to create a Treatment Rationale to indicate that the benefits of continuing clozapine treatment outweigh the risk of neutropenia when the patient has moderate neutropenia (ANC 500-999/μL for the general population) or severe neutropenia (ANC<500/μL for general population and patients with benign ethnic neutropenia).

How to Submit ANCs using the ANC Lab Reporting Form
ANCs may still be submitted via the *ANC Lab Reporting Form* online or via fax. • To submit online, log into your account at www.clozapinerems.com and select the Submit ANC Lab button. Enter information to find the patient and then select the Continue button. Enter the ANC Lab information and select the Save button. • To submit via fax, complete the ANC Lab Reporting Form and fax to 800-878-5927. The Patient Status Form must still be submitted monthly.

Certification Requirements	
Previous Requirement	**New Requirement**
	A pharmacy may now designate up to two authorized representatives.
Pharmacies must recertify every two years.	Pharmacies are no longer required to renew certification every two years. Now, every two years the pharmacy must confirm that the designated authorized representative is the same. If different, the pharmacy must re-certify with the new authorized representative.

Staff Training	
Previous Requirement	**New Requirement**
Pharmacy staff must complete the **Knowledge Assessment**.	Pharmacy staff are no longer required to complete the **Knowledge Assessment**. However, the authorized representative must still complete the **Knowledge Assessment.**

Website P M e ssage 1 – current website

New Cl a ine RE C m ng N v 15th

- ALL Prescribers and Pharmacies **must re certify** to continue to prescribe or dispense clozapine.
- ALL Patients continuing on clozapine **must be re enr lled** by a certified prescriber or prescriber designee.
- ***Start recertification and re-enrollment on August 16, 2021 to avoid interruption in patient treatment.***

  Go to www.newclozapinerems.com

  - Click on Log-in | Register tab. You need to create new login z credentials before re-certifying by clicking on Register.

Website p p p ss e e 2

New Cl z pine REMS Req ire nte

- ALL Pr scrib rs and Pharmaci s **st re-certify** to continu to pr scrib or disp ns clozapin .
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Important ro ram p ate – current website

DATE: Ne Clozapine REMS Comin November 15, 2021

Re-Certification and Re-Enrollment Required at www.newclozapinerems.com.

- ALL Prescribers and Pharmacies **must re-certify** to continue to prescribe or dispense clozapine.
- ALL Patients continuing on clozapine **must be re-enrolle** by a certified prescriber or prescriber designee.
- ***Start re-certification and re-enrollment on August 16, 2021 to avoid interruption in patient treatment***

  Go to www.newclozapinerems.com
  - Click on Log-in | Register tab. You need to create new login **w** credentials before re-certifying by clicking on Register.

CLOZAPINE REMS

What is the Clozapine RE

The Clozapine REMS (Risk Evaluation and Mitigation Strategy) is a safe
neutropenia associated with clozapine treatment.

Severe neutropenia (absolute neutrophil count (ANC) less than 500/uL

CLOZAPINE REMS

Contact the Clozapine REMS Conta

Phone

1-888-586-0758

Fax

1-800-878-5927

CLOZAPINE REMS

Find Retail Pharmaci

Locate a retail pharmacy certified to di

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Find Retail Pharmacies

OutPat Test Sub02 Pharmacy
22333 Jammie Squares
Philadelphia, PA 19002

XM Test Sub02 Pharmacy
22 Rittenhouse Square

CLOZAPINE REMS

Find Specialty Pharmacies

Specialty pharmacies certified to dispense clozapine.

OutPat Test Pharmacy

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CLOZAPINE REMS

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CLOZAPINE REMS

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CLOZAPINE REMS

Prescriber

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To certify as a presc

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Review the Prescribing Information

Review each drug's Prescribing Information

- Clozaril®
- Versacloz®
- Clozapine Tablets, USP (Accord Healthcare)
- Clozapine Tablets, USP (Aurobindo Pharma USA)
- Clozapine Tablets, USP (Aurobindo Pharma USA)
- Clozapine Tablets, USP (Aurobindo Pharma USA)
- Clozapine Tablets, USP (Mayne Pharma)
- Clozapine Tablets, USP (Mayne Pharma)
- Clozapine Tablets, USP (Mylan Pharmaceuticals)
- Clozapine ODT (Mylan Pharmaceuticals)
- Clozapine Tablets, USP (Mylan Pharmaceuticals)
- Clozapine Tablets, USP (Sun Pharmaceutical Indus
- Clozapine Tablets, USP (Teva Pharmaceuticals USA
- Clozapine Tablets, USP (Teva Pharmaceuticals USA

CLOZAPINE REMS

Pharmacy

Pharmacies must be certified in the Clozapine REMS t

To certify your pha

1

Designate an Authorized Representative

Designate an authorized representative to carry out
implementation and compliance with the Clozapine R

2

Review the Pharmacy Information

Have the authorized representative review the Cloza
Guide for Pharmacists.

3

Complete the Knowledge Assessment for P

Have the authorized representative successfully com
Pharmacy and submit it to the Clozapine REMS.

Online or

Establish Processes and Procedures

CLOZAPINE REMS

Patient

To receive treatment, a patient must be

Patient

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Talk With Your Clozapine Doct

Review A Guide for Patients and Care

Neutropenia with your doctor.

2

Ask Questions!

CLOZAPINE REMS

Patient

To receive treatment, a

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CLOZAPINE REMS

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CLOZAPINE REMS

Patient

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CLOZAPINE REMS

Prescriber

1310000001

Prescriber Certification

You are currently certified in the Clozapine REMS.

Edit Personnel

Edit, Add, or Remove Designees from the Clozapine R

Enroll Patients in the Clozapine REMS

You must enroll your patients in the Clozapine REMS

Manage Patients

Manage your Clozapine REMS patients.

Prescriber

1310000000

Prescriber Certification

You must certify in the Clozapine REMS to prescribe clozapine. To certify please complete the following:

1 **Review the clozapine prescribing information:**

- Clozaril®
- Versacloz®
- Clozapine Tablets, USP (Accord Healthcare)
- Clozapine Tablets, USP (Aurobindo Pharma USA)
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- Clozapine Tablets, USP (Teva Pharmaceuticals USA)
- Clozapine Tablets, USP (Teva Pharmaceuticals USA)
- Clozapine Tablets, USP (Teva Pharmaceuticals USA)

2 **Review the Guide for Healthcare Providers**

Review the Clozapine and the Risk of Neutropenia: A Guide for Prescribers.

3 **Complete the Knowledge Assessment for Prescribers**

Successfully complete the Knowledge Assessment for Prescribers and submit it to the Clozapine REMS.

Online or Print

4 **Complete the Prescriber Enrollment Form**

Enroll in the Clozapine REMS by completing the Prescriber Enrollment Form and submitting it to the Clozapine REMS.

Online or Print

Prescriber Office Personnel Management

Edit, Add, Remove Designees from the Clozapine REMS

→ Manage Designees

Enroll Patients in the Clozapine REMS

You must enroll your patients in the Clozapine REMS.

→ Enroll Patient

Manage Patients

Manage your Clozapine REMS patients.

→ Manage Patients

Prescriber Materials

- Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers
- Knowledge Assessment for Prescribers
- Prescriber Enrollment Form
- Patient Enrollment Form
- Patient Status Form
- ANC Lab Reporting Form
- Prescriber Designee Enrollment Form
- What's Changed in the Clozapine REMS for Prescribers?

Upload Form

Uploads must be in PDF format.

Browse Or drop files here

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Edit, Add, Remove Designees from the Clozapine REMS

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→ Enroll Patient

Manage Patients

Manage your Clozapine REMS patients.

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Upload Form

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Browse Or drop files here

CLOZAPINE REMS

Prescriber - Knowledge Assessment

Knowledge Assessment for Prescribers

You may leave and return to the Knowledge Assessment at any time, your progress w

0 of 12 questions in progress

1 . All clozapine products are only available under the single shared Clozapine REM

- ◯ True
- ◯ False

2 . Clozapine is associated with severe neutropenia, which can lead to serious infec

- ◯ True
- ◯ False

3 . Severe neutropenia is defined as:

- ◯ A. A white blood cell count (WBC) less than 2000/μL
- ◯ B. An absolute neutrophil count (ANC) less than 1000/μL

Prescriber - Knowledge Assessment

Knowledge Assessment for Prescribers

You may leave and return to the Knowledge Assessment at any time, your progress will be saved.

Knowledge Assessment Incomplete : All questions must be answered correctly to pass the Knowledge Assessment. You may retry the Knowledge Assessment.

3 correct answers out of 13 (Failed)

1 . All clozapine products are only available under the single shared Clozapine REMS. ✕

- ○ True
- ◉ False

2 . Clozapine is associated with severe neutropenia, which can lead to serious infection and death. ✕

- ○ True
- ◉ False

3 . Severe neutropenia is defined as: ✕

- ○ A. A white blood cell count (WBC) less than 2000/µL
- ○ B. An absolute neutrophil count (ANC) less than 1000/µL
- ○ C. An absolute neutrophil count (ANC) less than 500/µL
- ◉ D. None of the above

4 . Before initiating treatment with clozapine: ✕

- ○ A. A baseline absolute neutrophil count (ANC) must be at least 1000/µL for a patient with documented benign ethnic neutroper (BEN)
- ◉ B. A baseline absolute neutrophil count (ANC) must be at least 1500/µL for a patient who is part of the general population (i.e., patient does not have documented BEN)
- ○ C. A baseline absolute neutrophil count (ANC) is not necessary
- ○ D. Both A and B

CLOZAPINE REMS

Prescriber - Knowledge Assessment

Knowledge Assessment for Prescribers

You may leave and return to the Knowledge Assessment at any time, your progress w

Home

Knowledge Assessment Complete

12 correct answers out of 1

1 . All clozapine products are only available under the single shared Clozapine REM

- (•) True
- ( ) False

2 . Clozapine is associated with severe neutropenia, which can lead to serious infec

- (•) True
- ( ) False

CLOZAPINE REMS

Manage Patients

Manage Patients
Manage your Clozapine REMS patients.

Show 10 entries

Edit	Name Date of Birth	REMS Patient ID	Population	N
	PatientPat Smithe 06/27/1954	CPDemoPatDiscont	General	N
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	PatientPat Smith 06/27/1954	CMDemoInt01	General	3
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	PatientPat Smithe 06/27/1954	CMDemoMonthly	General	M
	PatientPat Smith 07/15/1965	CPPatEg30Cl37	General	W

CLOZAPINE REMS

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ANC Lab Reporting Form

Patient ANC Monitoring

This form may be used by certified prescribers and their designees to sul
requirement (using the Patient Status Form).

Note: Report of an ANC lab value indicating moderate (general population) or severe neutropenia (general or BEN population) requires treatment to be interrupted or discontinued or the creation of a Treatment Rationale by the prescriber unless a more recent ANC lab value is provided that is ≥ 1000/µL for a general population patient or ≥ 500/µL for a BEN population patient.

and

Secti

Patient (Population: General)

Name:	PatientPat Smith
Date of Birth:	6/27/1954
REMS Patient ID:	CMDemo3xLate

Monitoring History

Show 10 entries

Date	Monitoring Activity
02/26/2021	Monitoring Frequency - 3 times a week

Showing 1 to 1 of 1 entries

CLOZAPINE REMS

ANC Lab Reporting Form

Patient ANC Monitoring

This form may be used by certified prescribers and their designees to sul
requirement (using the Patient Status Form).

Patient (Population: General)

Name: PatientPat Smith
Date of Birth: 6/27/1954
REMS Patient ID: CMDemoWeekly

Monitoring History

Show 10 entries

Date	Monitoring Activity
03/28/2021	Monitoring Frequency - Weekly
03/29/2021	ANC Lab Value - Normal Range (≥ 1500/µL)
04/05/2021	ANC Lab Value - Normal Range (≥ 1500/µL)

Showing 1 to 3 of 3 entries

ANC Entry

Current Patient Monitoring Frequency: Weekly

CLOZAPINE REMS

Ho

Patient Enrollment

Note: Only a certified prescriber may enroll a Benign Ethnic Neutropenia (BEN) patient or a hospice patient.

and

Section

Patient Enrollment

First Name

First Name

Last Name

Last Name

Gender

◯ Male ◯ Female ◯ Other

Date of Birth

mm/dd/yyyy

Race

◯ American Indian or Alaska Native ◯ Asian ◯ Black or African American ◯

◯ Other

Ethnicity

◯ Hispanic or Latino ◯ Not Hispanic or Latino

Phone

Phone

Email

Email

☐ Does the patient have a permanent address?

Zip Code

CLOZAPINE REMS

Patient Enrollment

Patient Enrollment

First Name

First Name

Last Name

Last Name

Gender

◯ Male ◯ Female ◯ Other

Date of Birth

mm/dd/yyyy

Race

◯ American Indian or Alaska Native ◯ Asian ◯ Black or African American ◯

◯ Other

Ethnicity

◯ Hispanic or Latino ◯ Not Hispanic or Latino

Phone

Phone

Email

Email

☐ Does the patient have a permanent address?

Zip Code

Patient Information

Is this patient actively on clozapine therapy?

CLOZAPINE REMS

Patient Status Form (PSF)

Patient Status Form (PSF)

Assess the patient by obtaining complete blood counts, including the absolute neu
This form must be completed monthly for each patient continuing treatment with

Note: Report of an ANC lab value indicating moderate (general population) or severe neutropenia (general or BEN population) requires treatment to be interrupted or discontinued or the creation of a Treatment Rationale by the prescriber unless a more recent ANC lab value is provided that is ≥ 1000/μL for a general population patient or ≥ 500/μL for a BEN population patient. and

Se

Patient (Population: General)

Name:	PatientTerry Smitt
Date of Birth:	9/22/1989
REMS Patient ID:	CMDemoEvy2Wk

Patient Status

Are you monitoring the patient as recommended in the Prescribing Informati

○ Yes ◉ No

Monitoring

Current Patient Monitoring Frequency: Every 2 weeks

Hosp

For hosp

CLOZAPINE REMS

Patient Status Form (PSF)

Patient Status Form (PSF)

Assess the patient by obtaining complete blood counts, including the absolute neu
This form must be completed monthly for each patient continuing treatment with

Patient (Population: General)

Name:	PatientTerry Smitt
Date of Birth:	9/22/1989
REMS Patient ID:	CMDemoEvy2Wk

Patient Status

Are you monitoring the patient as recommended in the Prescribing Informatio

◯ Yes ◉ No

Monitoring

Current Patient Monitoring Frequency: Every 2 weeks

Change the patient's monitoring frequency to:

Frequency

Daily | Weekly | Monthly

Or

Hosp

For hosp
expectar
monitor
patient a

I want t
every 6

☐ This

CLOZAPINE REMS

Assess the patient by obtaining complete blood counts, including the absolute neu
This form must be completed monthly for each patient continuing treatment with

Patient ()

Name:
Date of Birth:
REMS Patient ID:

Patient Status

Are you monitoring the patient as recommended in the Prescribing Informati

○ Yes ◉ No

Monitoring

Current Patient Monitoring Frequency: 0

Change the patient's monitoring frequency to:

Frequency

Daily Weekly Monthly

Or

Hosp

For hosp
expecta
monitor
patient a

I want t
every 6

☐ This

Did the patient experience any adverse event(s) due to clozapine-induced neu

CLOZAPINE REMS

ANC Lab Rep

Patient ANC Mon
This form may be u
requirement (usin

Patient

Name: PatientP
Date of Birth: 6/27/19
REMS Patient ID: CM3579

ANC (pe

WBC cou

0.0

Segs

0%

Bands

0%

CLOZAPINE REMS

Prescriber

PRJane PRDoe

Prescriber

Individual NPI Number

1310000000

Individual

DEA Numb

First Name

PRJane

Middle Initial

Middle Initial

Clinic/Practice Name

Test Prescriber Practice

Credentials

(•) MD ( ) NP ( ) PA ( ) DO ( ) Other

Address Line 1

12 Parker Avenue

Address Li

Address Li

City

Chambersburg

Number

420-689-9443

Extension

nnn...

Fax

209-772-0961

In general, what is the best time to contact you?

Preferred

CLOZAPINE REMS

Prescriber Office Personnel Managemen

PRJane PRDoe

PRJane PRDoe
Prescriber
Enrolled: 15th July, 2014

Prescriber Office Personnel Management
Edit, Add, Remove Designees from the Clozapine REMS

Show 10 entries

Action	Role	Name	Email
		PRJohn DesigneeSmith	PRDesignee@Examo

Delete Edit Designee

Showing 1 to 1 of 1 entries

CLOZAPINE REMS

CLOZAPINE REMS

Prescriber Office Personnel Management

Additional Designees

How will this designee interact with the Clozapine REMS?

- ◯ Allow this designee to be authorized to perform functions on my behalf via the Clozapine REM not be able to perform functions on my behalf via the Clozapine REMS website.
- ◯ Allow this designee to create login credentials for the Clozapine REMS website. The designee functions on my behalf via the Clozapine REMS Contact Center.

CLOZAPINE REMS

Prescriber Office Personnel Management

Additional Designees

How will this designee interact with the Clozapine REMS?

- (●) Allow this designee to be authorized to perform functions on my behalf via the Cloz not be able to perform functions on my behalf via the Clozapine REMS website.
- ( ) Allow this designee to create login credentials for the Clozapine REMS website. The functions on my behalf via the Clozapine REMS Contact Center.

For a designee who will only interact via the Clozapine REMS Contact Center, please download and s to the Clozapine REMS either via upload or fax to 1-800-878-5927

CLOZAPINE REMS

Prescriber Office Personnel Management

Additional Designees

How will this designee interact with the Clozapine REMS?

- ○ Allow this designee to be authorized to perform functions on my behalf via the Clozapine REM not be able to perform functions on my behalf via the Clozapine REMS website.
- ◉ Allow this designee to create login credentials for the Clozapine REMS website. The designee functions on my behalf via the Clozapine REMS Contact Center.

First Name | **Last Name** | **Titl**

First Name | Last Name | Ti

Phone | **Ext.** | **Fax**

Phone | Ext. | Fax

Email

Email

CLOZAPINE REMS

Pharmacy

Outpatient Pharmacy Group

To certify your pharmacy:

Your pharmacy is currently certified.

Obtain a Patient's REMS Dispense Authoriz

An RDA is a receipt from the Clozapine REMS signify
dispense for this patient are currently met.

Submit a Patient's ANC Lab Value

Pharmacists in possession of a patient's ANC lab valu
Clozapine REMS. A submitted ANC lab will be visible
pharmacy personnel attempting to obtain an RDA.

Pharmacy Personnel

Pharmacy

Outpatient Pharmacy

To certify your pharmacy:

Your pharmacy must certify in the Clozapine REMS to dispense clozapine. To certify please complete the following:

1 Review the Pharmacy Information

Have the authorized representative review the Clozapine and the Risk of Neutropenia: A Guide for Pharmacists.

2 Complete the Knowledge Assessment for Pharmacies

Have the authorized representative successfully complete the Knowledge Assessment for Pharmacy and submit it to the Clozapine REMS.

Online or Print

3 Enroll Pharmacy

→ Sign and Submit

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are currently met.

→ Obtain Patient RDA

Submit a Patient's ANC Lab Value

Pharmacists in possession of a patient's ANC lab value are encouraged to enter it into the Clozapine REMS. A submitted ANC lab will be visible to the patient's prescriber and pharmacy personnel attempting to obtain an RDA.

→ Submit ANC Lab

Pharmacy Personnel

A pharmacy can have multiple personnel with online accounts. You may invite personnel or remove them.

→ Manage Personnel

Pharmacies

A pharmacy can have multiple pharmacies grouped together under the responsibility of a Pharmacy Authorized Representative.

→ Manage Pharmacies

Pharmacy Materials

- Clozapine and the Risk of Neutropenia: A Guide for Pharmacists
- Knowledge Assessment for Pharmacies
- Inpatient Pharmacy Enrollment Form
- Outpatient Pharmacy Enrollment Form
- ANC Lab Reporting Form
- RDA Factsheet for Inpatient Pharmacies
- RDA Factsheet for Outpatient Pharmacies
- What's Changed in the Clozapine REMS for Pharmacies?

Upload Form

Uploads must be in PDF format.

Browse Or drop files here

Pharmacy

Outpatient Pharmacy

To certify your pharmacy:

Your pharmacy must certify in the Clozapine REMS to dispense clozapine. To certify please complete the following:

1 **Review the Pharmacy Information**

Have the authorized representative review the Clozapine and the Risk of Neutropenia: A Guide for Pharmacists.

2 **Complete the Knowledge Assessment for Pharmacies**

Have the authorized representative successfully complete the Knowledge Assessment for Pharmacy and submit it to the Clozapine REMS.

Online or Print

3 Enroll Pharmacy

Have the authorized representative enroll in the Clozapine REMS by completing the Pharmacy Enrollment Form and submitting it to the Clozapine REMS.

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are currently met.

→ Obtain Patient RDA

Submit a Patient's ANC Lab Value

Pharmacists in possession of a patient's ANC lab value are encouraged to enter it into the Clozapine REMS. A submitted ANC lab will be visible to the patient's prescriber and pharmacy personnel attempting to obtain an RDA.

→ Submit ANC Lab

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Browse Or drop files he

Pharmacy

Outpatient Pharmacy

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3 **Enroll Pharmacy**

→ Sign and Submit

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→ Obtain Patient RDA

Submit a Patient's ANC Lab Value

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→ Submit ANC Lab

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→ Manage Pharmacies

Pharmacy Materials

- Clozapine and the Risk of Neutropenia: A Guide for Pharmacists
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- ANC Lab Reporting Form
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- RDA Factsheet for Outpatient Pharmacies
- What's Changed in the Clozapine REMS for Pharmacies?

Upload Form

Uploads must be in PDF format.

Browse | Or drop files her

CLOZAPINE REMS

Pharmacy Enrollment

The authorized representative for the pharmacy must:

1. Review the REMS materials
2. Successfully complete the *Knowledge Assessment for Pharmacies*
3. Complete and submit this Pharmacy Enrollment, along with the completed *Kno*
4. Implement the necessary staff training and processes to comply with the REMS

Pharmacy Information

Organizational NPI Number

Use organizational NPI to populate form:	Organizational NPI Number

Pharmacy Name

Pharmacy Name

Address Line 1

Address Line 1

City

City

Number	Extension	Fax
nnn-nnn-nnnn	nnn...	Fax

The name, location, and phone number of your pharmacy will be publicly available o
the Clozapine REMS Contact Center at 1-888-586-0758

CLOZAPINE REMS

Pharmacy Enrollment

The authorized representative for the pharmacy must:

1. Review the REMS materials
2. Successfully complete the *Knowledge Assessment for Pharmacies*
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Pharmacy Information

Organizational NPI Number

Use organizational NPI to populate form:	Organizational NPI Number

Pharmacy Name

Pharmacy Name

Address Line 1

Address Line 1

City

City

Number	Extension	Fax
nnn-nnn-nnnn	nnn...	Fax

The name, location, and phone number of your pharmacy will be publicly available o
the Clozapine REMS Contact Center at 1-888-586-0758

CLOZAPINE REMS

Pharmacy - Knowledge Assessment

Knowledge Assessment for Pharmacies

You may leave and return to the Knowledge Assessment at any time, your progre

0 of 13 questions in progress

1 . All clozapine products are only available under the single shared Clozapine

- ◯ True
- ◯ False

2 . Clozapine is associated with severe neutropenia, which can lead to serious i

- ◯ True
- ◯ False

3 . Severe neutropenia is defined as:

- ◯ A. A white blood cell count (WBC) less than 2000/µL
- ◯ B. An absolute neutrophil count (ANC) less than 1000/µL

Pharmacy - Knowledge Assessment

Knowledge Assessment for Pharmacies

You may leave and return to the Knowledge Assessment at any time, your progress will be saved.

Try Again | Home

Knowledge Assessment Incomplete: All questions must be answered correctly to pass the Knowledge Assessment. You may retry the Knowledge Assessment.

1 correct answers out of 13 (Failed)

1. All clozapine products are only available under the single shared Clozapine REMS. ✕

- ○ True
- ◉ False

2. Clozapine is associated with severe neutropenia, which can lead to serious infection and death. ✕

- ○ True
- ◉ False

3. Severe neutropenia is defined as: ✕

- ○ A. A white blood cell count (WBC) less than 2000/µL
- ◉ B. An absolute neutrophil count (ANC) less than 1000/µL
- ○ C. An absolute neutrophil count (ANC) less than 500/µL
- ○ D. None of the above

4. Before initiating treatment with clozapine: ✕

- ○ A. A baseline absolute neutrophil count (ANC) must be at least 1000/µL for a patient with documented benign ethnic neutropenia (BEN)
- ◉ B. A baseline absolute neutrophil count (ANC) must be at least 1500/µL for a patient who is part of the general population (i.e., the patient does not have documented BEN)
- ○ C. A baseline absolute neutrophil count (ANC) is not necessary
- ○ D. Both A and B

5. Before clozapine treatment initiation, a certified prescriber must: ✕

- ○ A. Determine if the patient has documented BEN
- ○ B. Enroll the patient in the Clozapine REMS
- ◉ C. Counsel the patient/caregiver about the risk of severe neutropenia
- ○ D. Order blood work to obtain an ANC
- ○ E. Review the ANC and submit it to the Clozapine REMS
- ○ F. All of the above

CLOZAPINE REMS

Pharmacy - Knowledge Assessment

Knowledge Assessment for Pharmacies

You may leave and return to the Knowledge Assessment at any time, your progre

Home

Knowledge Assessment Complete

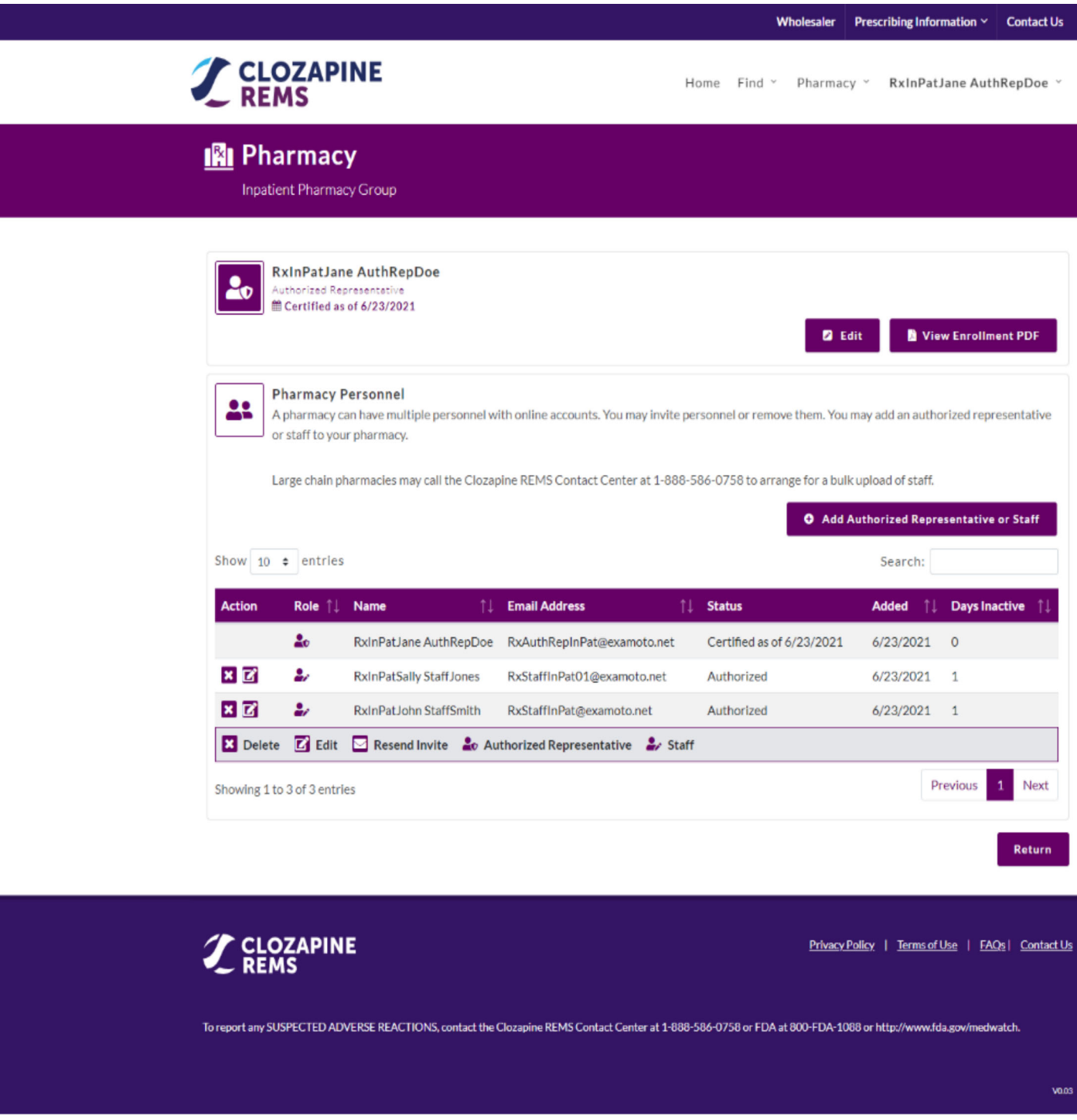
13 correct answers out

1 . All clozapine products are only available under the single shared Clozapine

- (●) True
- ( ) False

2 . Clozapine is associated with severe neutropenia, which can lead to serious i

- (●) True
- ( ) False


Wholesaler
Prescribing Information
Contact Us
CLOZAPINE REMS
Home
Find
Pharmacy
RxInPatJane AuthRepDoe
Pharmacy
Inpatient Pharmacy Group
RxInPatJane AuthRepDoe
Authorized Representative
Certified as of 6/23/2021
Edit
View Enrollment PDF
Pharmacy Personnel
A pharmacy can have multiple personnel with online accounts. You may invite personnel or remove them. You may add an authorized representative or staff to your pharmacy.
Large chain pharmacies may call the Clozapine REMS Contact Center at 1-888-586-0758 to arrange for a bulk upload of staff.
Add Authorized Representative or Staff
Show 10 entries
Search:
Action
Role
Name
Email Address
Status
Added
Days Inactive
RxInPatJane AuthRepDoe
RxAuthRepInPat@examoto.net
Certified as of 6/23/2021
6/23/2021
0
RxInPatSally StaffJones
RxStaffInPat01@examoto.net
Authorized
6/23/2021
1
RxInPatJohn StaffSmith
RxStaffInPat@examoto.net
Authorized
6/23/2021
1
Delete
Edit
Resend Invite
Authorized Representative
Staff
Showing 1 to 3 of 3 entries
Previous
1
Next
Return
CLOZAPINE REMS
Privacy Policy
Terms of Use
FAQs
Contact Us
To report any SUSPECTED ADVERSE REACTIONS, contact the Clozapine REMS Contact Center at 1-888-586-0758 or FDA at 800-FDA-1088 or http://www.fda.gov/medwatch.
V0.03

Pharmacy

Outpatient Pharmacy

Additional Staff

Personnel Type:

- ○ Authorized Representative
- ◉ Pharmacy Staff

Pharmacy Staff Information

Email

Email

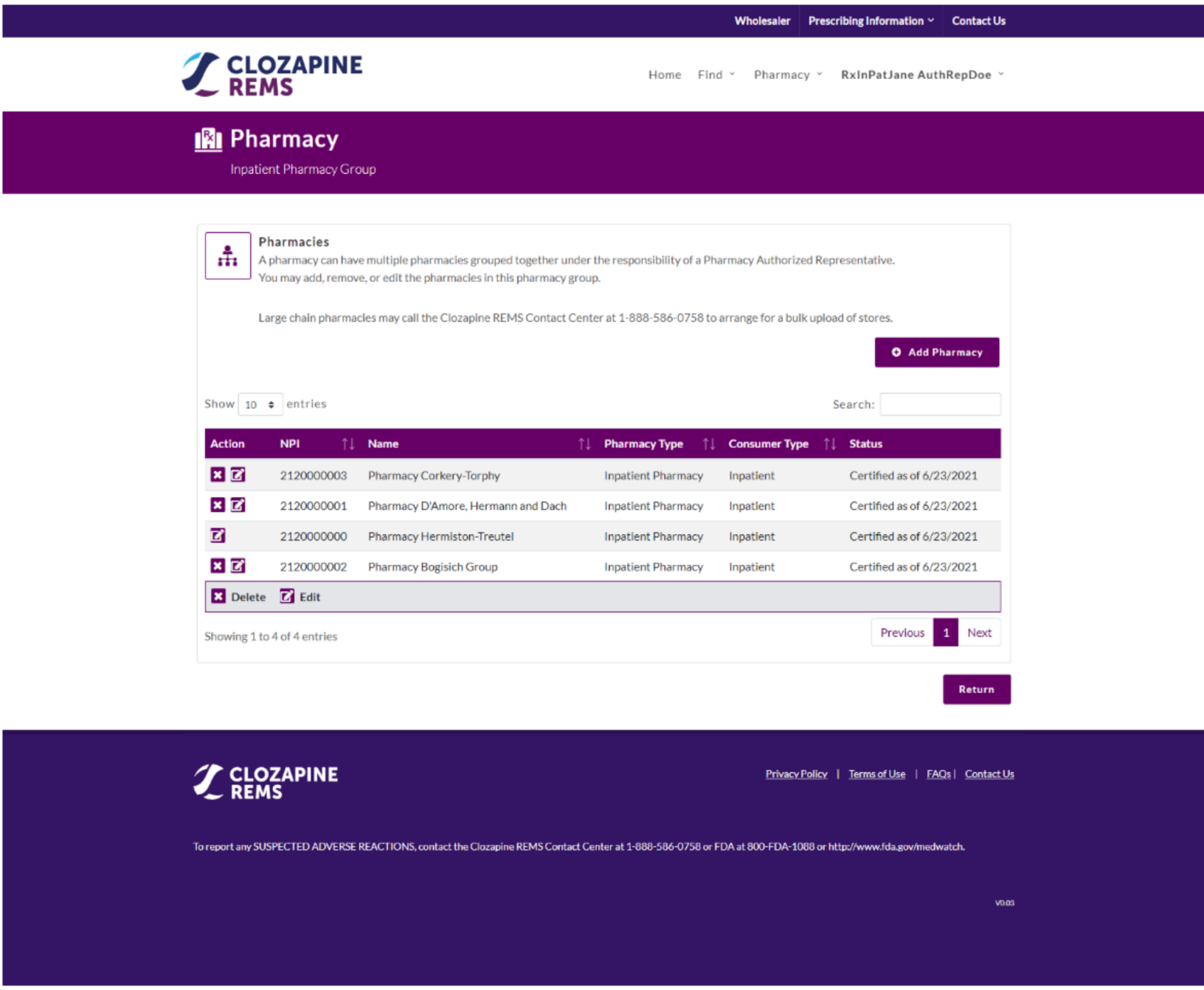
First Name | **Last Name** | **Title**

First Name | Last Name | Title

Phone | **Ext.** | **Fax**

Phone | Ext. | Fax

Ca


Wholesaler
Prescribing Information
Contact Us
CLOZAPINE REMS
Home
Find
Pharmacy
RxInPatJane AuthRepDoe
Pharmacy
Inpatient Pharmacy Group
Pharmacies
A pharmacy can have multiple pharmacies grouped together under the responsibility of a Pharmacy Authorized Representative.
You may add, remove, or edit the pharmacies in this pharmacy group.
Large chain pharmacies may call the Clozapine REMS Contact Center at 1-888-586-0758 to arrange for a bulk upload of stores.
Add Pharmacy
Show 10 entries
Search:
Action
NPI
Name
Pharmacy Type
Consumer Type
Status
2120000003 Pharmacy Corkery-Torphy Inpatient Pharmacy Inpatient Certified as of 6/23/2021
2120000001 Pharmacy D'Amore, Hermann and Dach Inpatient Pharmacy Inpatient Certified as of 6/23/2021
2120000000 Pharmacy Hermiston-Treutel Inpatient Pharmacy Inpatient Certified as of 6/23/2021
2120000002 Pharmacy Bogisich Group Inpatient Pharmacy Inpatient Certified as of 6/23/2021
Delete
Edit
Showing 1 to 4 of 4 entries
Previous
1
Next
Return
CLOZAPINE REMS
Privacy Policy | Terms of Use | FAQs | Contact Us
To report any SUSPECTED ADVERSE REACTIONS, contact the Clozapine REMS Contact Center at 1-888-586-0758 or FDA at 800-FDA-1088 or http://www.fda.gov/medwatch.
V0.03

Pharmacy

Outpatient Pharmacy

Additional Pharmacy

Organizational NPI Number

Use organizational NPI to populate form: | Organizational NPI Number

(Select address type to populate form)

○ Office Address ○ Mailing Address

Pharmacy Name

Pharmacy Name

DEA N

DEA

Address Line 1

Address Line 1

Address Line 2

Address Line 2

City

City

State

State

Number

nnn-nnn-nnnn

Extension

nnn...

Fax

Fax

Pharmacy

Outpatient Pharmacy

Submit a Patient's ANC Lab Value

Pharmacists in possession of a patient's ANC lab value are encouraged to enter it into the Clozapine REMS. A submitted patient's prescriber and pharmacy personnel attempting to obtain an RDA.

Find an enrolled patient:

1 **Find a patient by entering the patient's information below:**

First Name	Last Name	Date of Birth
First Name	Last Name	mm/dd/yyyy

REMS Patient ID	Phone Or Email
REMS Patient ID	Phone Or Email

Can

Pharmacy

Outpatient Pharmacy

Submit a Patient's ANC Lab Value

Pharmacists in possession of a patient's ANC lab value are encouraged to enter it into the Clozapine REMS. A submitted A
patient's prescriber and pharmacy personnel attempting to obtain an RDA.

Patient (Population: General)

Name:	PatientHospPat Smith	Zip Code:	52722
Date of Birth:	6/27/1954	Phone:	920-723-63
REMS Patient ID:	CPPatEg30Cg180	Email:	CPHspPatEg

Monitoring History

Date	Monitoring Activity
03/28/2021	Monitoring Frequency - Monthly
09/04/2020	ANC Lab Value - Mild Neutropenia (1000 to 1499/µL)

ANC Entry

Current Patient Monitoring Frequency: Monthly

Blood Draw Date

MM/DD/YYYY

General Patient Population

- ○ Normal Range (≥ 1500/µL)
- ○ Mild Neutropenia (1000 to 1499/µL)
- ○ Moderate Neutropenia (500 to 999/µL)
- ○ Severe Neutropenia (< 500/µL)

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are cu

Find an enrolled patient:

1 **Find a patient by entering the patient's information below:**

First Name	Last Name	Date of Birth
First Name	Last Name	mm/dd/yyyy

REMS Patient ID	Phone Or Email
REMS Patient ID	Phone Or Email

Can

CLOZAPINE REMS

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirem

Find an enrolled patient:

1 **Find a patient by entering the patient's information below:**

First Name

First Name

Last Name

XXXXXXXXXXX

REMS Patient ID

Phone Or Email

CLOZAPINE REMS

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirem

Find an enrolled patient:

1 **Find a patient by entering the patient's information below:**

First Name

First Name

Last Name

Smith

REMS Patient ID

Phone Or Email

CLOZAPINE REMS

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

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Find an enrolled patient:

1 **Find a patient by entering the patient's information below:**

First Name

First Name

Last Name

Smitt

REMS Patient ID

Phone Or Email

CLOZAPINE REMS

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirem

Find an enrolled patient:

1 **Find a patient by entering the patient's information below:**

First Name

First Name

Last Name

Smitt

REMS Patient ID

Phone Or Email

CLOZAPINE REMS

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirem

Patient

Name:	PatientTerry Smitt
Date of Birth:	9/22/1989
REMS Patient ID:	CP1378924

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are cu

Patient (Population: General)

Name:	PatientTerry Smitt	Zip Code:	28601
Date of Birth:	9/22/1989	Phone:	920-723-
REMS Patient ID:	CPPatEI30NoC	Email:	CPPatEI3

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REM
obtaining an RDA, retain it as your receipt.

RDA: a620091f Copy Print

Obtained by RxOutPatJane AuthRepDoe on 04/13/2021 at 11:57 AM Coordinated Universal Time

⊕ Detail

Dispensing Information

Outpatients should be dispensed a days' supply in accordance with their monitoring frequency.

Date	Manufacturer	NDC Code	Days' Supply	Quantity
mm/dd/yyyy	Manufacturers	NDC Codes		

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are curr

Patient (Population: General)

Name:	PatientTerry Smitt	Zip Code:	28601
Date of Birth:	9/22/1989	Phone:	920-723-63
REMS Patient ID:	CPPatEI30NoC	Email:	CPPatEI30I

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REMS obtaining an RDA, retain it as your receipt.

RDA: a620091f Copy Print

Obtained by RxOutPatJane AuthRepDoe on 04/13/2021 at 11:57 AM Coordinated Universal Time

Detail

Safe Use Conditions:

- Patient is Enrolled: PatientTerry Smitt
- Pharmacy is Certified

Dispensing Information

Outpatients should be dispensed a days' supply in accordance with their monitoring frequency.

Date	Manufacturer	NDC Code	Days' Supply	Quantity
mm/dd/yyyy	Manufacturers	NDC Codes		

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are curr

Patient (Population: General)

Name:	PatientPat Smith	Zip Code:	52722
Date of Birth:	7/15/1965	Phone:	920-722-9(
REMS Patient ID:	CPPatEg30CI37	Email:	CPPatEg30

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REMS obtaining an RDA, retain it as your receipt.

RDA: cc4d99ef Copy Print

Obtained by RxOutPatJane AuthRepDoe on 04/13/2021 at 12:30 PM Coordinated Universal Time

Detail

Safe Use Conditions:

- Patient is Enrolled: PatientPat Smith
- Patient, PatientPat Smith, has a current Patient Status Form (PSF) on file indicating the patient is continuing treatment.
- Pharmacy is Certified

Dispensing Information

Outpatients should be dispensed a days' supply in accordance with their monitoring frequency.

Date	Manufacturer	NDC Code	Days' Supply	Quantity
mm/dd/yyyy	Manufacturers	NDC Codes		

Pharmacy

Outpatient Pharmacy

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An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are cu

Patient (Population: General)

Name:	PatientPat Smithe	Zip Code:	44145
Date of Birth:	6/27/1954	Phone:	204-896-
REMS Patient ID:	CPDemoPatDiscont	Email:	CPPatDis

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REM
obtaining an RDA, retain it as your receipt.

DO NOT DISPENSE

⊕ Detail

Safe Use Conditions:

- ✓ Patient is Enrolled: PatientPat Smithe
- ✗ Patient, PatientPat Smithe, most recent Patient Status Form (PSF) on file indicates the patient has discontinued treatment.
  their prescriber has not authorized a refill and to contact their prescriber if necessary.
- ✓ Pharmacy is Certified

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are cu

Patient (Population: General)

Name:	PatientAli Smithson	Zip Code:	35405
Date of Birth:	4/4/1962	Phone:	920-727-
REMS Patient ID:	CPPatInterupt	Email:	CPPatInte

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REM obtaining an RDA, retain it as your receipt.

DO NOT DISPENSE

⊕ Detail

Safe Use Conditions:

- ✓ Patient is Enrolled: PatientAli Smithson
- ✗ Patient, PatientAli Smithson, most recent Patient Status Form (PSF) on file indicates the patient has interrupted treatment. their prescriber has not authorized a refill and to contact their prescriber if necessary.
- ✓ Pharmacy is Certified

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are curr

Patient (Population: General)

Name:	PatientPat Smith	Zip Code:	52722
Date of Birth:	6/27/1954	Phone:	920-723-63
REMS Patient ID:	CPPatEg30Cg37	Email:	CPPatEg30

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REMS obtaining an RDA, retain it as your receipt.

DO NOT DISPENSE

Detail

Safe Use Conditions:

- ✓ Patient is Enrolled: PatientPat Smith
- ✗ Patient, PatientPat Smith, does NOT have a current Patient Status Form (PSF) on file. If you have a current ANC Lab value, yo Dispense Rationale for this patient below.
- ✓ Pharmacy is Certified

Recent Monitoring History

Date	Monitoring Activity
03/28/2021	Monitoring Frequency - Monthly
03/25/2021	ANC Lab Value - Mild Neutropenia (1000 to 1499/µL)
03/10/2021	ANC Lab Value - Not Reported(Clinician Discretion)
02/24/2021	ANC Lab Value - Normal Range (≥ 1500/µL)
02/17/2021	ANC Lab Value - Not Reported(Clinician Discretion)

Showing 1 to 5 of 7 entries

Previous 1 2 Next

Pharmacy Dispense Rationale I

Prescriber NPI on patient's s

Blood Draw Date

MM/DD/YYYY

ANC (per µL)

0

Request D

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are cu

Patient (Population: General)

Name:	PatientHospPat Smith	Zip Code:	52722
Date of Birth:	6/27/1954	Phone:	920-723-
REMS Patient ID:	CPPatEg30Cg180	Email:	CPHspPat

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REM
obtaining an RDA, retain it as your receipt.

DO NOT DISPENSE

⊕ Detail

Safe Use Conditions:

- ✓ Patient is Enrolled: PatientHospPat Smith
- ✓ General population Patient, PatientHospPat Smith, has a Dispense Rationale with an ANC greater than 999 per µl.
- ✓ Pharmacy is Certified
- ✗ Patient, PatientHospPat Smith, has a reached the Dispense Rationale limit. Please contact the patient's prescriber, the pres Patient Status Form (PSF) for this patient to receive drug.
- ✓ Prescriber is Certified: PRJane PRDoe

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are cu

Patient (Population: General)

Name:	PatientTerry Smitt	Zip Code:	28601
Date of Birth:	9/22/1989	Phone:	920-723-
REMS Patient ID:	CPPatEI30NoC	Email:	CPPatEI3

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REM obtaining an RDA, retain it as your receipt.

RDA: ee9ad14d Copy Print

Obtained by RxOutPatJane AuthRepDoe on 04/13/2021 at 12:25 PM Coordinated Universal Time

Detail

Prescription dispense recorded for this RDA.

Pharmacy

Outpatient Pharmacy

Obtain a Patient's REMS Dispense Authorization (RDA)

An RDA is a receipt from the Clozapine REMS signifying that the REMS requirements to dispense for this patient are cu

Patient (Population: General)

Name:	PatientTerry Smitt	Zip Code:	28601
Date of Birth:	9/22/1989	Phone:	920-723-
REMS Patient ID:	CPPatEI30NoC	Email:	CPPatEI3

REMS Dispense Authorization (RDA)

A REMS Dispense Authorization is a receipt from the Clozapine REMS indicating that the safe use conditions managed by the REM
obtaining an RDA, retain it as your receipt.

× RDA Reversed.

This is a r r s a i f a M l c r ic r c rd ha was sig d l c r ically. F ll wi g his ar ma if s a i s f a y a d all l c r ic sig a ur s f r his l c r ic r c rd.

/s/ M

MLEAH HART
07/26/2021 06:39:17 P

BARBARA A BERGQUIST M
07/26/2021 06:44:33 P

CAROLYN N TIEU on behalf of KATE H OSWELL
07/26/2021 06:53:19 P

CAROLYN N TIEU
07/26/2021 06:53:47 P

CYNTHIA L LACIVITA
07/26/2021 08:29:45 P M

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s098

SUMMARY REVIEW

U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
DIVISION OF PSYCHIATRY PRODUCTS

NDA/BLA #s: NDA 19758
Products: Clozaril (clozapine HCl) 25 mg and 100 mg Tablets.
APPLICANT: HERITAGE LIFE SCIENCES
FROM: Marc Stone, M.D. Deputy Director for Safety
DATE: July 28, 2021

The REMS for clozapine products, of which Clozaril is a member, was originally approved on September 15, 2015, and the most recent REMS modification was approved on February 18, 2021. The REMS consists of elements to assure safe use an implementation system, and a timetable for submission of assessments of the REMS.

On July 16, 2020, the applicant submitted proposed modifications to the REMS which include changes to the frequency of the submission of patient monitoring via a new Patient Status Form (PSF) and changes to the pharmacy operations to verify safe use conditions for a REMS dispense authorization and changes to the goal of the REMS. You also proposed additional minor changes to the operation of the REMS program, including certain changes to the audit frequency and information dissemination requirements. When this modification is approved, the prescriber or prescriber designee will no longer need to submit ANC results every 7, 15, or 31 days depending on the patient's monitoring frequency. Instead, they will be required to fill out a monthly PSF to report ANC results. On this form, prescribers will be able to authorize continuation of the drug if the patient has an ANC that falls below the acceptable range as described in the Prescribing Information. The PSF will also be used to report adverse events due to clozapine-induced neutropenia which would assist our goal of mitigating the risk of severe neutropenia.
After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the sponsor submitted an adequate rationale to support the proposed modifications described above.

We have determined that the third part of the goal of the REMS must be modified from "ensuring compliance with the monitoring schedule for absolute neutrophil count (ANC) prior to dispensing clozapine" to "ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia." This goal was revised to minimize treatment interruptions.

The modified REMS now consists of: elements to assure safe use, including healthcare providers are specially certified, pharmacies that dispense the drug are specially certified, the drug is dispensed to patients with evidence or other documentation of safe-use conditions, each patient using the drug is subject to certain monitoring, and each patient using the drug is enrolled in a registry, an implementation system, and a timetable for submission of assessments of the REMS.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERMIAS ZERISLASSIE
07/28/2021 12:19:58 PM

MARC B STONE
07/28/2021 01:09:00 PM