

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019758Orig1s061

Trade Name: CLORAZIL

Generic or Proper Name: (clozapine)

Sponsor: Heritage Life Science Barbados INC.

Approval Date: September 15, 2015

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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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019758Orig1s061

APPROVAL LETTER



NDA 019758/S-061/S-077

SUPPLEMENTAL APPROVAL

HLS Therapeutics USA, Inc. e
Attention: Gilbert Godin, COO
919 Conestoga Road
Building 3, Suite 310
Rosemont, PA 19010

Dear Mr. Godin:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 19, 2008 (S-061), and August 14, 2015 (S-077) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Clozaril (clozapine) 25 mg and 100 mg Tablets.

We also acknowledge receipt of your amendments to Supplement 061 dated May, 5, 2009, September 28, 2012, October 18, 2013, September 25, 2014, January 7, 2015, April 23, 2015, May 15, 2015, July 17, 2015, September 4, 2015, and September 14, 2015.

The “Prior Approval” supplemental new drug application, S-077 provides for changes to the Contraindications, Boxed Warning, Warnings and Precautions, Dosage and Administration, and Use in Specific Populations sections of the labeling to update the neutropenia monitoring algorithms and associated Clozaril (clozapine) treatment recommendations; and to accommodate for Clozaril (clozapine) treatment for patients with benign ethnic neutropenia.

The “Prior Approval” supplemental new drug application S-061 provides for a proposed risk evaluation and mitigation strategy (REMS) for Clozaril (clozapine) and was submitted in accordance with section 909(b)(3) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified Clozaril (clozapine) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

OVER APPROVAL & ABERRANT

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. e

CONTENT OF LABELING

As soon as possible, but not later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314. 0(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/CDER/industry/IndustryDataStandards/structuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled " SPL Standard for Content of Labeling Technical Questions and Answers" at <http://www.fda.gov/oc/ohrt/CDER/industry/IndustryDataStandards/structuredProductLabeling/default.htm>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314. 0(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked up copy that shows all changes, as well as a clean Microsoft Word version. The marked up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Under section 909(b)(1) of FDAAA, we identified Clazril as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 27, 2007, elements to assure safe use required under 21 CFR 314. 20. Under section 909(b)(3), you were required to submit a proposed REMS for Clazril.

Your proposed REMS, submitted September 19, 2007, last amended on September 14, 2011, and appended to this letter, is approved. The REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

The REMS will use a shared system for the ETASU, the implementation system, and the REMS assessments. This shared system, known as the Clazril REMS Program, includes the products listed on the FDA REMS website, available at <http://www.fda.gov/remss>. Other products may be added in the future if additional NDAs or ANDAs are approved.

The approval of the REMS is concurrent with the approval of new labeling language, which is not supported by the existing standard regulatory systems (the “legacy risk management systems”). To support continued treatment of patients during the Clozapine REMS Program 90 day transition period, this REMS includes the following requirements:

1. For 30 calendar days after the date of this letter,
 - a. Prescribers and pharmacies must continue to use the legacy risk management systems for certification, patient enrollment, and monitoring, including reporting of ANC values.
 - b. All legacy risk management system requirements remain in effect.
2. Beginning 30 calendar days after the date of this letter,
 - a. All clozapine patient registry websites under the legacy risk management systems must automatically redirect to the Clozapine REMS Program website.
 - b. All phone and fax numbers previously associated with standard clozapine patient registries under the legacy risk management systems must automatically transfer to the Clozapine REMS Program.
 - c. The Clozapine REMS Program must be fully functional, with the following exceptions:
 - i. Electronic telecommunication verification that allows a pharmacy or group of pharmacies to receive electronic authorization to dispense through a pharmacy network or pharmacy switch will not be available.
 - ii. Pre-Dispense Authorizations will not be available.
 - iii. Wholesalers and distributors must distribute only to pharmacies either enrolled in a registry under a legacy risk management system or certified in the Clozapine REMS program.
 - iv. Prescribers who are certified under a legacy clozapine risk management program may continue to prescribe clozapine without immediately becoming certified in the Clozapine REMS Program, but may only provide prescriptions to the existing patients who are continuing uninterrupted treatment begun under one of the legacy risk management systems. Prescribers must enroll in the Clozapine REMS Program to prescribe for any other patients.
3. Beginning 72 calendar days after the date of this letter, all prescribers must be certified in the Clozapine REMS program to prescribe clozapine for any patient.
4. Beginning 90 calendar days after the date of this letter, all elements of the Clozapine REMS Program must be fully implemented and functional in accordance with the approved REMS.

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

A. Background REMS Program Implementation and Operations

1. REMS Program Utilization

a) Pharmacies, Prescribers, Prescriber Designees and Distributors

- (1) Number of each stakeholder, status of certification or enrollment (as applicable), and method of certification or enrollment (as applicable)

m m a (2) Summary of reasons certification or enrollment is incomplete for each stakeholder (Examples include "Pharmacy unable to configure pharmacy management system," "Prescriber missing information for," etc.)

b) Patient Status by Patient Type (General population, BEN patients, NNRMF patients, hospice patients)

- (1) Active
(2) Interrupted
(3) Discontinued

2. Contact Center Report

a) Number of Contacts

b) Summary of reason for call (Examples include "Enrollment question," "Lab query," etc.) by reporter (i.e. pharmacy, prescriber, patient)

c) Narrative of any corrective actions resulting from issues identified

3. Clozapine REMS Program Compliance (to be included beginning with the 12 Month REMS Assessment Report)

a) Audits

m m a (1) Summary of audit findings for audits conducted during the reporting period.
(2) Summary of corrective actions taken to address findings, the status of the corrective actions, and any resulting preventative actions that were taken

m b b) Number of clozapine prescriptions dispensed that were written by non-certified prescribers (reported or detected through audit)

- (1) Actions taken (Examples include "Provision of clozapine program materials", "Prescriber become certified", etc.)
(2) Outcome of actions taken

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

d) Number of shipments sent to noncertified pharmacies, source of report, and actions taken to prevent future occurrences

e) Number of times clozapine prescription dispensed because a pharmacy bypassed REMS audits and if any such events occurred, describe how these events were identified, the root cause of the failure, and any corrective actions taken (reported or detected through audit). Stratify by pharmacy

- type (switch vs non switch)
- f) Noncompliance with the Clozapine REMS Program requirements, source of report, and any corrective action or resolution
 - (1) Number of PDAs without ANC (excluding hospice patients) and number of these resulting in clozapine dispensing
 - (2) Number of PDAs without treatment rationales provided when ANC unacceptable, and number of these resulting in clozapine dispensing
- 4 Barriers or Delays in Patient Access
- a) False negatives: e g , all entities are certified, but system generated a prescription rejection notice
 - b) Inadvertent enrollment deactivations, or failures to notify enrollees of forthcoming enrollment expirations
 - c) Reported lack of certified prescribers and or pharmacies in a patient's local area
 - d) Unintended system interruptions and resolutions
 - e) For PDAs via electronic verification: Number of times and reasons a manual back up system was used to validate a prescription and source of problem (e g , switch level, pharmacy level, REMS database, etc)

Inappropriate Patient Access

- a) Inpatient pharmacy dispensing for outpatient use (reported or detected through audit)
- b) False positives: e g , one or all entities were not certified but system verified dispensing generated a PDA

B Evaluation of Safe Use Behaviors

- 1 Prescription Rejections
 - a) Number of pre dispense authorizations (PDAs) that did not encounter any REMS related rejections prior to being authorized
 - b) Total number of authorizations that encountered any REMS related rejections
 - c) Mean, median, and range of the duration of time to authorize
 - d) Provide reasons for prescription rejections stratified by type of PDA (via pharmacy management system or clozapine REMS) and duration of time to authorize prescription if initially rejected
- 2 Treatment Rationales
 - a) Number of treatment rationales submitted, stratified by type
 - b) Mean number of treatment rationales submitted per prescriber
- 3 Number of notifications and alerts sent, stratified by type and stakeholder type (Prescriber, Pharmacy)

C Evaluation of Knowledge Survey

- 1 An evaluation of knowledge of certified prescribers of the risk of severe

- neutropenia, appropriate monitoring of clozapine, and the REMS requirements and
2. An evaluation of knowledge of authorized representatives and pharmacists of the risk of severe neutropenia, appropriate monitoring of clozapine, and REMS requirements
 3. An evaluation of knowledge of patients or caregivers of the risk of severe neutropenia, and appropriate monitoring of clozapine

D. Evaluation of Required Monitoring

1. Total instances of severe neutropenia for unique patients (reported as lowest ANC for each unique patient whose ANC drops below 500 μL within each month) and
2. Total instances of neutropenia for unique patients (reported as lowest ANC for each unique patient whose ANC drops below 1,000 μL within each month)

E. With respect to each goal included in the REMS, an assessment of the extent to which the approved REMS, including each element of the REMS, is meeting the goal or whether one or more such goals or such elements should be modified.

F. The Clozapine REMS Program Transition Status (to be included in the 6 Month REMS Assessment Report only)

1. Date when REMS materials became available to healthcare professionals on the website and via the contact center
2. Dates healthcare professionals could become certified online, by mail, and by fax
3. Automatic data transition:
 - a) Total number of prescribers automatically transitioned into the Clozapine REMS Program (i.e. who were associated with a patient with a valid ANC or WBC lab value within the past 3 years), and date the transition was complete
 - b) Total number of prescriber designees automatically transitioned into the Clozapine REMS Program (i.e. who were associated with a patient with a valid ANC or WBC lab value within the past 3 years), and date the transition was complete
 - c) Number of pharmacies automatically transitioned into the Clozapine REMS Program (i.e. who were associated with a patient with a valid ANC or WBC lab value in one or more of the individual clozapine patient registries within the past 3 years), and date the transition was complete
 - d) Total number of patients transferred into the Clozapine REMS Registry (must have a valid ANC or WBC lab value in one or more of the individual clozapine patient registries within the past 3 years)
 - e) Number of patients automatically transitioned into the Clozapine REMS Registry who previously were on the National Non Rechallenge Master File (NNRMF), and the number that have been flagged as such in the Registry and
 - f) Dates individual clozapine patient registry websites began redirecting

visitors to the Clozapine R MS Program

- G. Clozapine R MS Program Outreach and Communication (to be included in the 6 and 12 Month R MS Assessment Report only)
1. Dates of distribution of the Dear HCP Letter, Dear Distributor Letter, Dear Professional Society Letter and the numbers sent on each date. Provide a list of the documents included with each distribution including the revision date.
 2. Number of undeliverable and returned communications for each distribution date, by method of distribution
 3. A summary of the Clozapine R MS Program website utilization
- H. Knowledge Assessments (to be included in the 6 and 12 Month R MS Assessment Report only)
1. Number of completed Knowledge Assessment for Healthcare Providers (KAs) for certified prescriber and pharmacy authorized representative, and pharmacy staff that have elected to take the KA, including method of enrollment and number of attempts to complete, by stakeholder
 2. Summary of the most frequently missed KA questions, stratified by prescriber and pharmacy
 3. A summary of potential comprehension or perception issues identified with the KA
 4. Proposed remediation for Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers and or the Knowledge Assessment for Healthcare Providers

We remind you that in addition to the R MS assessments submitted according to the timetable in the approved R MS, you must include an adequate rationale to support a proposed R M modification for the addition, modification, or removal of any of goal or element of the R MS, as described in section 301(g)(4) of the FDCA.

We also remind you that you must submit a R MS assessment when you submit a supplemental application for a new indication for use as described in section 301(g)(2)(A). 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 R MS;
- 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 R MS.
- 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 the 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 rationale 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 submissions 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 019758 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

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 301(f)(1) 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 301(b)(2) or (j). A violation of this provision in 301(f) could result in enforcement action.

Prominently identify the 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 019758 REMS ASSESSMENT d

**NEW SUPPLEMENT FOR ND 019758/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR ND 019758/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR ND 019758/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR ND 019758/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If 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 ND 019758

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send two copies of REMS related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock up form with annotated references, and (3) the package insert(s) to: A

Food and Drug Administration

Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
901 B Ammendale Road
Beltville, MD 20701-1266

You must submit final promotional material and package insert(), accompanied by a Form FDA 223, at the time of initial dissemination or publication [21 CFR 314.1(b)(3)(i)]. Form FDA 223 is available at

<http://www.fda.gov/download/AboutFDA/ReportManualForms/FormUCM037070.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/download/AboutFDA/ReportManualForms/FormUCM37114.pdf>. For

more information about submission of promotional material to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CenterOffice/CDER/ucm090142.htm>.

SPECIAL REPORTING FOR NEUTROPENIA ADVERSE EVENTS

In your email communication dated April 9, 2011, you agreed to the following special reporting for neutropenia adverse event : s

1. Expedite case of neutropenia with an ANC <1000 μ L (i.e., submit the case as a 1 day Alert report) that would not normally be required to be submitted because severe neutropenia is a labeled event. This special reporting applies to cases collected by the registry, as well as cases spontaneously reported to an individual sponsor.
2. Review, prepare, and submit the 1 day Alert report as described under 21 CFR 314.10, which include conducting follow up (21 CFR 314.10(c)(1)(ii)).
3. Have written procedure for identifying an adverse event report meeting the criteria (serious and non-serious outcome for all cases of neutropenia with an ANC <1000 μ L) and submitting the 1 day Alert report to FDA.

We also request that clozapine sponsor have a procedure for identifying a reportable sponsor when an adverse event report is received for a clozapine product and the sponsor is unknown. There must be a reportable sponsor identified to conduct follow up and submit the report to FDA.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.10 and 314.11). s

If you have any questions, contact Ann Sohn, Regulatory Project Manager, at (301) 796 2232 or email at ann.sohn@fda.hhs.gov.

in reply,

{See appended electronic signature page}

Michelle V. Mathis, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE :
Content of Labeling
REMS
REMS Program Materials c

This is a s a io of a l c o ic co d ha was sig d
l c o ically a d his ag is h ma if s a io of h l c o ic
sig a u .

/s/ E

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09/15/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019758Orig1s061

LABELING

HIGHLIGHTS **SCIBING IN ONMATI**

These highlights do not include all the information needed to use

- CL A IL®** safely and effectively. See full prescribing information for **CLOZARIL**.
- CL A IL®** (clozapine) tablets, or oral use
- Initial U.S. Approval: 1989

WARNING: SEVERE NEUTROPENIA; THOUSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPES; SEIZURES; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED SYMPTOMS

See full prescribing information for complete boxed warning.

- Severe Neutropenia:** **CLOZARIL** can cause severe neutropenia, which can lead to serious and fatal infections. Patients initiating and continuing treatment with **CLOZARIL** must have a baseline blood absolute neutrophil count (ANC) measured before treatment initiation and regular ANC monitoring during treatment (2.1, 5.1).
- CLOZARIL** is available only through a restricted program called the Clozapine MS (5.2).
- Thostatic Hypotension, Bradycardia, and Syncope:** Risk is dose-related. Starting dose is 12.5 mg. Titrate gradually and use divided dosages (2.2, 2.5, 5.3).
- Seizure:** Risk is dose-related. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors or seizure (2.2, 5.4).
- Myocarditis and Cardiomyopathy:** Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions (5.5).
- Increased Mortality in Elderly Patients with Dementia-Related Symptoms:** **CLOZARIL** is not approved for this condition (5.6).

CONTINUED CHANGES

- Indications and Usage (1.1) f 09/2015
- Boxed Warning, Severe Neutropenia f f 09/2015
- Dosage and Administration, Required Laboratory Testing Prior to Initiation and During Therapy (2.1), Discontinuation of Treatment (2.4) 9/2015
- Contraindications, History of Clozapine-induced Agranulocytosis or Severe Granulocytopenia (4), Hypersensitivity (4.1) 9/2015
- Warnings and Precautions, Severe Neutropenia (5.1), Clozapine REMS Program (5.2) f 9/2015

INDICATIONS AND USAGE

CLOZARIL is an atypical antipsychotic indicated for:

- Treatment-resistant schizophrenia. Efficacy was established in an active-controlled study (1.1, 14.1).
- Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. Efficacy was established in an active-controlled study (1.2, 14.2).

DOSE AND ADMINISTRATION

- Starting Dose: 12.5 mg once daily or twice daily (2.2).
- Use cautious titration and divided dosage schedule (2.2, 5.3).
- Titration: increase the total daily dosage in increments of 25 mg to 50 mg per day, if well-tolerated (2.2).
- Target dose: 300 mg to 450 mg per day, in divided doses, by the end of 2 weeks (2.2).
- Subsequent increases: increase in increments of 100 mg or less, once or twice weekly (2.2)
- Maximum daily dose: 900 mg (2.2).

DOSE FORMS AND STRENGTHS

25 mg and 100 mg tablets with a facilitated score on one side (3)

CONTRAINDICATIONS

- Known serious hypersensitivity to clozapine or any other component of CLOZARIL (4.2).

WARNINGS AND PRECAUTIONS

- Eosinophilia:** Assess for organ involvement (e.g., myocarditis, pancreatitis, hepatitis, colitis, nephritis). Discontinue if these occur (5.7).
- QT Interval Prolongation:** Can be fatal. Consider additional risk factors for prolonged QT interval (disorders and drugs) (5.8).
- Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. These metabolic changes include:
 - Hyperglycemia and Diabetes Mellitus:** Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes (5.9).
 - Dyslipidemia:** Undesirable alterations in lipids have occurred in patients treated with atypical antipsychotics. (5.9).
 - Weight Gain:** Significant weight gain has occurred. Monitor weight gain. (5.9).
- Neuroleptic Malignant Syndrome (NMS):** Immediately discontinue and monitor closely. Assess for co-morbid conditions (5.10).
- Fever:** Evaluate for infection and for neutropenia, NMS (5.11).
- Pulmonary Embolism (PE):** Consider PE if respiratory distress, chest, pain, or deep-vein thrombosis occur (5.12).
- Anticholinergic Toxicity:** Use cautiously in presence of specific conditions (e.g., narrow angle glaucoma, use of anticholinergic drugs) (5.13).
- Interference with Cognitive and Motor Performance:** Advise caution when operating machinery, including automobiles (5.14).

ADVERSE REACTIONS

Most common adverse reactions (≥5%) were: CNS reactions (sedation, dizziness/vertigo, headache, and tremor); cardiovascular reactions (tachycardia, hypotension, and syncope); autonomic nervous system reactions (hypersalivation, sweating, dry mouth, and visual disturbances); gastrointestinal reactions (constipation and nausea); and fever (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact **HLS Therapeutics (USA), Inc. at (844) 457-8721 or DA at 1-800-DA-1088 or www.da.gov/medwatch**

DRUG INTERACTIONS

- Concomitant use of **Strong CYP1A2 Inhibitors:** Reduce CLOZARIL dose to one third when coadministered with strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, enoxacin) (2.6, 7.1).
- Concomitant use of **Strong CYP3A4 Inducers** is not recommended (2.6, 7.1).
- Discontinuation of CYP1A2 or CYP3A4 Inducers:** Consider reducing CLOZARIL dose when CYP1A2 (e.g., tobacco smoke) or CYP3A4 inducers (e.g., carbamazepine) are discontinued (2.6, 7.1).

USE IN SPECIFIC POPULATIONS

- Nursing Mothers:** Discontinue drug or discontinue nursing, taking into consideration importance of drug to mother (8.3).

See 17 for **ADDITIONAL INFORMATION**

Revised: 09/2015

FULL PRESCRIBING INFORMATION ONLY *

WARNING: EVERESTROPEA; ORTHOSTATIC HYPOTENSION; RADIATION; ADYPOSE; EZURE; MYOCARDITIS; ARDAMYOPATHY; REACTIONS; MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PHOSPHOS

1 INDICATIONS AND USAGE

- 1.1 Treatment-Resistant Schizophrenia
- 1.2 Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders

2 DOSAGE AND ADMINISTRATION

- 2.1 Required Laboratory Testing Prior to Initiation and During Therapy
- 2.2 Dosing Information
- 2.3 Maintenance Treatment
- 2.4 Discontinuation of Treatment
- 2.5 Re-Initiation of Treatment
- 2.6 Dosage Adjustment with Concomitant use of CYP1A2, CYP2D6, CYP3A4 Inhibitors or CYP1A2, CYP3A4 Inducers
- 2.7 Renal or Hepatic Impairment, or CYP2D6 Poor Metabolizers

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- 5.1 Severe Neutropenia
- 5.2 **lozapine REMS Program**
- 5.3 Orthostatic Hypotension, Bradycardia, and Syncope
- 5.4 Seizures
- 5.5 Myocarditis and Cardiomyopathy
- 5.6 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- 5.7 Eosinophilia
- 5.8 QT Interval Prolongation
- 5.9 Metabolic Changes
- 5.10 Neuroleptic Malignant Syndrome
- 5.11 Fever
- 5.12 Pulmonary Embolism
- 5.13 Anticholinergic Toxicity
- 5.14 Interference with Cognitive and Motor Performance
- 5.15 Tardive Dyskinesia
- 5.16 Cerebrovascular Adverse Reactions

- 5.17 Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation of CLOZARIL

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Potential for Other Drugs to Affect CLOZARIL
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WARNING: SEVERE NEUTROPHENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURES; MYOCARDITIS AND CARDIOMYOPATHY; REDUCED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Severe Neutropenia

LOZAR L treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/ μ L. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with LOZAR L a baseline ANC must be at least 1500/ μ L for the general population; and must be at least 1000/ μ L for patients with documented benign Ethnic Neutropenia (EN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat) [see *Dosage and Administration (2.1) and Warnings and Precautions (5.1)*].

Because of the risk of severe neutropenia, LOZAR L is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the lozapine REMS Program. [see *Warnings and Precautions (5.2)*].

Orthostatic Hypotension, Bradycardia, Syncope

Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with LOZAR L treatment. The risk is highest during the initial titration period, particularly with rapid dose escalation. These reactions can occur with the first dose, with doses as low as 12.5 mg per day. Initiate treatment at 12.5 mg once or twice daily; titrate slowly; and use divided dosages. Use LOZAR L cautiously in patients with cardiovascular or cerebrovascular disease or conditions predisposing to hypotension (e.g., dehydration, use of antihypertensive medications) [see *Dosage and Administration (2.2, and 2.5) and Warnings and Precautions (5.3)*].

Seizures

Seizures have occurred with LOZAR L treatment. The risk is dose-related. Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing. Use caution when administering LOZAR L to patients with a history of seizures or other predisposing risk factors for seizure (e.g., pathology, medications that lower the seizure threshold, alcohol abuse). Caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others [see *Dosage and Administration (2.2), Warnings and Precautions (5.4)*].

Myocarditis and Cardiomyopathy

Fatal myocarditis and cardiomyopathy have occurred with LOZAR L treatment. Discontinue LOZAR L and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with clozapine-related myocarditis or cardiomyopathy should not be rechallenged with LOZAR L. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or

ECG changes occur [see Warnings and Precautions (5.6)].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CLOZARIL is not approved for use in patients with dementia-related psychosis [see Warnings and Precautions (5.6)].

1 INDICATIONS AND USAGE

1.1 Treatment-Resistant Schizophrenia

CLOZARIL is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. Because of the risks of severe neutropenia and of seizure associated with its use, CLOZARIL should be used only in patients who have failed to respond adequately to standard antipsychotic treatment [see Warnings and Precautions (5.1, 5.4)].

The effectiveness of CLOZARIL in treatment-resistant schizophrenia was demonstrated in a 6-week, randomized, double-blind, active-controlled study comparing CLOZARIL and chlorpromazine in patients who had failed other antipsychotics [see Clinical Studies (14.1)].

1.2 Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder

CLOZARIL is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at risk for death.

The effectiveness of CLOZARIL in reducing the risk of recurrent suicidal behavior was demonstrated over a two-year treatment period in the InterSePT™ trial [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Required Laboratory Tests Prior to Initiation and During Therapy

Prior to initiating treatment with CLOZARIL, a baseline ANC must be obtained. The baseline ANC must be at least 1500/ μ L for the general population, and at least 1000/ μ L for patients with documented Benign Ethnic Neutropenia (BEN). To continue treatment, the ANC must be monitored regularly [see Warnings and Precautions (5.1)]. 5

2.2 Dose Titration

The starting dose is 12.5 mg once daily or twice daily. The total daily dose can be increased in increments of 25 mg to 50 mg per day, if well-tolerated, to achieve a target dose of 300 mg to 450 mg per day (administered in divided doses) by the end of 2 weeks. Subsequently, the dose can be increased once weekly or twice weekly in increments of 100 mg to 100 mg. The maximum dose is 900 mg per day. To minimize the risk of orthostatic hypotension, bradycardia, and syncope, it is necessary to use this low starting dose, gradual titration schedule, and divided dosages [see Warnings and Precautions (5.3)].

CLOZARIL can be taken with or without food [see Pharmacokinetics (12.3)].

2.3 Maintenance Treatment

Generally, patients responding to CLOZARIL should continue maintenance treatment on their effective dose beyond the acute episode.

2.4 Discontinuation of Treatment

Method of treatment discontinuation will vary depending on the patient's last ANC:

- See Tables 2 or 3 for appropriate ANC monitoring based on the level of neutropenia if abrupt treatment discontinuation is necessary because of moderate to severe neutropenia.
- Reduce the dose gradually over a period of 1 to 2 weeks if termination of CLOZARIL therapy is planned and there is no evidence of moderate to severe neutropenia.
- 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 $\geq 1500/\mu\text{L}$ and for BEN patients until their ANC is $\geq 1000/\mu\text{L}$ or above their baseline.
- Additional ANC monitoring is required for any patient reporting onset of fever (temperature of 38.5°C or 101.3°F , or greater) during the 2 weeks after discontinuation [see Warnings and Precautions (5.1)].
- 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.

2.5 Re-initiation of Treatment

When restarting CLOZARIL in patients who have discontinued CLOZARIL (i.e., 2 days or more since the last dose), re-initiate with 12.5 mg once daily or twice daily. This is necessary to minimize the risk of hypotension, bradycardia, and syncope [see Warnings and Precautions (5.3)]. If that dose is well-tolerated, the dose may be increased to the previously therapeutic dose as quickly as recommended for initial treatment. m

2.6. Drugs with potential to inhibit CYP2D6, CYP3A4 and CYP3A5

Drugs that may be used in patients with known or suspected CYP2D6 and CYP3A4 inhibitors (e.g., fluoxetine, ciprofloxacin, dextromethorphan, duloxetine, venlafaxine, escitalopram, erythromycin, bupropion, fluoxetine, paroxetine, duloxetine, nefazodone, St. John's wort (hypericum perforatum)) are listed in Table 2.6.1. [See Drug Interactions]

Table 2.6.1: Drugs with potential to inhibit CYP2D6, CYP3A4 and CYP3A5

Concomitant drug	Substrate		
	Inhibitor CYP2D6 or CYP3A4/5	Additive co-inhibitor with CYP2D6 or CYP3A4/5	Displacement co-inhibitor with CYP2D6 or CYP3A4/5
Strong CYP2D6 Inhibitors	Use is contraindicated with CYP2D6 substrates		Indicates CYP2D6 substrate based on clinical response
Model weak CYP1A2 Inhibitors	Monitor for additive reduction in CYP2D6 or CYP3A4/5 need		Monitor for additive effect on CYP2D6 or CYP3A4/5 need
CYP2D6 or CYP3A4/5 Inhibitors			
Strong CYP3A4/5 Inducers	Concomitant use is not recommended. However, clinical data suggests the substrate may be clinically indicated. CYP2D6 or CYP3A4/5 substrate monitoring effect is possible		Reduce CYP2D6 or CYP3A4/5 dose based on clinical response
Model weak CYP1A2 or CYP3A4/5 Inducers	Monitor for additive effect on CYP2D6 or CYP3A4/5 if applicable		Monitor for additive reaction. Consider reduction in CYP2D6 or CYP3A4/5 need

2.7. Inhibition of CYP2D6 by other metabolites

It may be possible to identify CYP2D6 substrates with high clinical potential, hepatic impairment, and CYP2D6 or metabolite-based use is possible (8.1.1.1)

3 DOSAGE OR ADJUSTMENTS

CLOZARIL (clozapin) is available as 25 mg and 100 mg round, plain, uncoated tablets with a facilitated score on one side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

CLOZARIL is contraindicated in patients with a history of serious hypersensitivity to clozapin (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson Syndrome) or any other component of CLOZARIL [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Severe neutropenia

Background

CLOZARIL can cause neutropenia (a low absolute neutrophil count (ANC)), defined as a reduction below pre-treatment normal levels of blood neutrophils. The ANC is usually available as a component of the complete blood count (CBC), including differential, and is more relevant to drug-induced neutropenia than is the white blood cell (WBC) count. The ANC may also be calculated using the following formula: *ANC equals the Total WBC count multiplied by the total percentage of neutrophils obtained from the differential (neutrophil "segs" plus neutrophil "bands")*. Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary [see Adverse Reactions (6.2)]. Neutropenia may be mild, moderate, or severe (see Tables 2 and 3). To improve and standardize understanding, "severe neutropenia" replaces the previous terms severe leukopenia, severe granulocytopenia, or agranulocytosis.

Severe neutropenia, ANC less than (<) 500/ μ L, occurs in a small percentage of patients taking CLOZARIL and is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks on treatment and then declines. The mechanism by which CLOZARIL causes neutropenia is unknown and is not dose-dependent.

Two separate management algorithms are provided below, the first for patients in the general population, and the second for patients identified to have baseline neutropenia.

CLOZARIL Treatment and Monitoring in the General Patient Population (see Table 2)

Obtain a CBC, including the ANC value, prior to initiating treatment with CLOZARIL to ensure the presence of a normal baseline neutrophil count (equal to or greater than 1500/ μ L) and to permit later comparisons. Patients in the general population with an ANC equal to or greater than (\geq)1500/ μ L are considered within normal range (Table 2)

and are eligible for treatment. Weekly ANC monitoring is required for all patients during the first 6 months of treatment. If a patient's ANC remains equal to or greater than 100/ μ L for the first 6 months of treatment, monitoring frequency may be reduced every 2 weeks for the next 6 months. If the ANC remains equal to or greater than 100/ μ L for the second 6 months of combination therapy, ANC monitoring frequency may be reduced once every 4 weeks hereafter.

Table 2: CLOZARIL Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring for the General Patient Population

ANC Level	CLOZARIL Treatment Recommendations	ANC Monitoring
Normal range (≥1500/ μ L)	<ul style="list-style-type: none"> • In treatment • If ANC is less than 500/μL: <ul style="list-style-type: none"> - 5 30 days, 500/μL - 5 30 days, 500/μL 	<ul style="list-style-type: none"> • Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
	<ul style="list-style-type: none"> • Discontinue if ANC is less than 500/μL 	<ul style="list-style-type: none"> • See Section 2.4.5
Mild Neutropenia (1000 to 1499/ μ L)	<ul style="list-style-type: none"> • Continue treatment 	<ul style="list-style-type: none"> • These times weekly until ANC ≥1500/μL • Once ANC ≥1500/μL, refer to "Normal Range" ANC monitoring schedule
Moderate Neutropenia (500 to 999/ μ L)	<ul style="list-style-type: none"> • Recommend holding 1 cycle • In the event of suspected drug induced neutropenia • Resume treatment once ANC ≥1000/μL 	<ul style="list-style-type: none"> • Daily until ANC ≥1000/μL • These times weekly until ANC ≥1500/μL • Once ANC ≥1500/μL, refer to "Normal Range" ANC monitoring schedule
Severe Neutropenia (less than 500/ μ L)	<ul style="list-style-type: none"> • Recommend holding 1 cycle • In the event of suspected drug induced neutropenia 	<ul style="list-style-type: none"> • Daily until ANC ≥1000/μL • These times weekly until ANC ≥1500/μL • If patient develops febrile neutropenia

ANC Level	CL A L Treatment ecommendations	ANC Monitoring
	<ul style="list-style-type: none"> Do not echallenge unless p escibe dete mines benefits r outweigh risks 	resume t eatment as a new patient unde “No mal Range” monitoring once ANC $\geq 1500/\mu\text{L}$

* Confirm all initial reports of ANC less than $1500/\mu\text{L}$ with a repeat ANC measurement within 24 hours

** If clinically appropriate

CLOZARIL Treatment and Monitoring in Patients with Benign Ethnic Neutropenia (see Table 3)

Benign ethnic neutropenia (BEN) is a condition observed in certain ethnic groups whose average ANC values are lower than “standard” laboratory ranges for neutrophils. 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 dark 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 severe infections. They are not at increased risk for developing CLOZARIL-induced neutropenia. Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider hematology consultation before initiating or doing CLOZARIL treatment as necessary.

Patients with BEN require a different ANC algorithm for CLOZARIL management due to their lower baseline ANC levels. Table 3 provides guidelines for managing CLOZARIL treatment and ANC monitoring in patients with BEN.

Table 3: Patients with Benign Ethnic Neutropenia (BEN); CL A L Treatment ecommendations Based on Absolute Neutrophil Count (ANC) Monitoring

ANC Level	Treatment ecommendations	ANC Monitoring
Normal BEN range (Established ANC baseline $\geq 1000/\mu\text{L}$)	<ul style="list-style-type: none"> Obtain at least two baseline ANC levels before initiating treatment If treatment interrupted: <ul style="list-style-type: none"> < 30 days, continue monitoring as before ≥ 30 days, monitor as if new patient 	<ul style="list-style-type: none"> Weekly from initiation to 6 months Every 2 weeks from 6 to 12 months Monthly after 12 months
	<ul style="list-style-type: none"> Discontinuation of treatment for reasons other than neutropenia 	<ul style="list-style-type: none"> See Section 2.4

<p>BEN a Neu e ia a 500 999/μL* a</p>	<ul style="list-style-type: none"> • Recommend a hematology consultation a • • a Continue treatment a 	<ul style="list-style-type: none"> • Three times weekly until ANC \geq 1000/μL or \geq p tient's known baseline a • a Once a ANC \geq 1000/μL or a p tient's known baseline a check a ANC weekly for a week a then a return to p tient's last "Normal Range" ANC monitoring interval** a
<p>BEN Severe Neu e ia a less th n 500/μL* a</p>	<ul style="list-style-type: none"> • a Recommend a hematology consultation a • a Interrupt treatment for a suspected clozapine- a induced neutropenia a • a Do not a challenge a unless prescriber determines a benefit a outweighs a risk a 	<ul style="list-style-type: none"> • a Discontinue a ANC \geq 500/μL a then a • Three times weekly until a ANC \geq p tient's a baseline a • a If patient a challenged a resume a treatment a anew a p tient's a "Normal Range" a monitoring interval a once a ANC \geq 1000/μL or a p tient's a baseline a

* Confirm a II initial reports of ANC less th n 500/ μ L with a repeat a ANC measurement within a 24 hours a

** If clinically appropriate a

General Guidelines for Management of All Patients with Fever or with Neutropenia

- Fever: Interrupt CLOZARIL s p rec ution ry me sure in ny p tient who develops fever, defined s temper ture of 38.5°C [101.3°F] or gre ter, nd obt in n ANC level. Fever is often the first sign of neutropenic infection.
- ANC less th n 1000/ μ L: If fever occurs in ny p tient with n ANC less th n 1000/ μ L, initi te p propri te workup nd tre tment for infection nd refer to T bles 2 or 3 for m an gement.
- Consider hem tology consult tion.
- See Neuroleptic M ligh nt Syndrome [NMS] nd Fever under WARNINGS nd PRECAUTIONS (5) nd Instructions for P tients, under PATIENT COUNSELING INFORMATION (17).

Rechallenge after an ANC less than 500/ μ L (severe neutropenia)

For some p tients who experience severe CLOZARIL-rel ted neutropeni , the risk of serious psychi tric illness from discontinuing CLOZARIL tre tment m ay be gre ter th n the risk of rech llenge (e.g. p tients with severe schizophrenic illness who h ve no tre tment options other th n CLOZARIL). A hem tology consult tion m y be useful in

deciding challenge patients. In general, however, decision challenges with development of severe neutropenia with CLOZARIL clozapine product.

If patients will be challenged, the clinicians should consider scenarios provided in Tables 2 and 3, the patient's medical and psychiatric history, discussion with the patient and his/her caregiver about the benefits and risks of CLOZARIL challenge, and the severity and characteristics of the neutropenic episode.

Using CLOZARIL with Other Drugs Associated with Neutropenia

It is unclear if concurrent use of the drugs known to cause neutropenia increases the risk severity of CLOZARIL-induced neutropenia. There is no strong scientific information about CLOZARIL when used in patients concurrently with these drugs. If CLOZARIL is used concurrently with known drugs that cause neutropenia (e.g., some chemotherapeutic agents), consider monitoring patients more closely than recommended in the guidelines provided in Tables 2 and 3. Consult with the oncologist in patients receiving concurrent chemotherapy.

5.2 Clozapine REMS Program

CLOZARIL is only available through restricted program under REMS called the Clozapine REMS Program because of the risk of severe neutropenia.

Key elements of the Clozapine REMS Program include:

- Healthcare providers who prescribe CLOZARIL must be certified with the Program by enrolling and completing training
- Patients who receive CLOZARIL must be enrolled in the program and comply with the ANC testing and monitoring requirements
- Pharmacies dispensing CLOZARIL must be certified with the program by enrolling and completing training and must only dispense to patients who are eligible to receive CLOZARIL

For more information visit www.clozapine.ems.com 1-844-267-8678.

5.3 Orthostatic Hypotension, Bradycardia, and Syncope

Hypotension, bradycardia, syncope, and dizziness were associated with clozapine treatment. The risk is highest during initiation of treatment, particularly with rapid dose escalation. These effects can occur with the first dose, doses less than 12.5 mg. These effects can be fatal. The syndrome is consistent with neuroleptic malignant syndrome (NMS).

Patients must begin maximum dose of 12.5 mg once daily twice daily. The first daily dose can be increased in increments of 25 mg to 50 mg per day, if well-tolerated,

a target dose of 100 mg to 450 mg per day (a minimum in divided doses) by the end of 2 weeks. Subsequently, the dose can be increased weekly or twice weekly, in increments up to 100 mg. The maximum dose is 900 mg per day. Use caution and titrate in divided doses to help minimize the risk of extrapyramidal reactions [see *Dosage and Administration (2.2)*]. Consider using the lowest effective dose. When restarting patients who have had even a brief interval without CLOZARIL (i.e., 2 days or more since the last dose), re-initiate treatment at 12.5 mg once daily or twice daily [see *Dosage and Administration (2.5)*].

Use CLOZARIL cautiously in patients with cardiovascular disease (history of myocardial infarction, ischemia, heart failure, recent unexplained abnormality), cerebrovascular disease, and conditions which would predispose patients to hypotension (e.g., concomitant use of antihypertensive, orthostatic hypotension).

5.4 Seizures

Seizure has been estimated to occur in approximately 5% of patients with clonidine at a cumulative incidence of approximately 5%, based on the occurrence of seizures in 61 of 174 patients exposed to clonidine during its clinical testing prior to generic marketing (i.e., a crude rate of 5%). The risk of seizure is dose-related. Initiate treatment with a low dose (12.5 mg), titrate slowly, and use divided dosing.

Use caution when administering CLOZARIL to patients with a history of seizure or other predisposing risk factors for seizure (e.g., head trauma or other CNS pathology, uremia, infection that lowered the seizure threshold, alcohol abuse). Because of the substantial risk of seizure associated with CLOZARIL use, caution patients about engaging in any activity where sudden loss of consciousness could cause injury to themselves or others (e.g., driving an automobile, operating complex machinery, swimming, climbing).

5.5 Myocarditis and Cardiomyopathy

Myocarditis and cardiomyopathy have occurred with the use of CLOZARIL. The reactions can be fatal. Discontinue CLOZARIL and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy. Generally, patients with a history of clonidine-associated myocarditis or cardiomyopathy should not be rechallenged with CLOZARIL. However, if the benefits of CLOZARIL treatment outweigh the potential risk of recurrent myocarditis or cardiomyopathy, the clinician may consider rechallenging with CLOZARIL in consultation with a cardiologist, after a complete cardiac evaluation, and under close monitoring.

Consider the possibility of myocarditis or cardiomyopathy in patients receiving CLOZARIL who present with chest pain, dyspnea, persistent tachycardia at rest, palpitations, fever, flu-like symptoms, hypotension, other signs or symptoms of heart failure, electrocardiographic findings (low voltage, ST-T abnormalities, arrhythmia, Q waves, right axis deviation, and prolonged R wave progression). Myocarditis most recently presented

within the first two months of zapin treatment. Symptoms can be myopathy generally occur than clzapin-associated myopathy and usually after 8 weeks of treatment. However, myopathy and cardiomyopathy can occur at any period during treatment with LOZARIL. It is common to see symptoms such as malaise, myalgia, pleuritic chest pain, and lower extremity edema. Typical laboratory findings include elevated creatinine, elevated lactate dehydrogenase (LDH), elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), eosinophilia, and elevated prothrombin time (PT). The treatment of myopathy may depend on the clinical presentation, and cardiac imaging (echocardiogram, radionuclide scintigraphy, cardiac catheterization) may be available to evaluate the underlying etiology.

5.6 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of 17 placebo-controlled trials (median duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients between 1.6 to 1.7 times that in placebo-treated patients. Overall, in a typical 10-week controlled trial, the risk of death in drug-treated patients was about 4.5%, compared to about 2.6% in the placebo group. Although the cause of death was varied, most deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infection (e.g., pneumonia) in nature. Observational studies suggest that, unlike atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality in this population. The extent to which the finding of increased mortality in observational studies may be attributable to the antipsychotic drug appears to be mechanistic in the patient population.

LOZARIL is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.7. Eosinophilia

Eosinophilia, defined as a blood eosinophil count greater than 700/ μ L, has occurred with LOZARIL treatment. In clinical trials, approximately 1% of patients developed eosinophilia. Zapin-related eosinophilia usually occurs during the first month of treatment. In some patients, it has been associated with myocarditis, pancreatitis, hepatitis, colitis, and nephritis. Such organ involvement could be consistent with a drug action with eosinophilia and systemic symptoms syndrome (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS). In patients developing eosinophilia during LOZARIL treatment, evaluate promptly organ and systemic symptoms, such as a rash, all types of symptoms, myocarditis, and organ-specific disease associated with eosinophilia. In LOZARIL-related drug-induced hypersensitivity syndrome, discontinue LOZARIL immediately.

LOZARIL treatment, evaluate promptly organ and systemic symptoms, such as a rash, all types of symptoms, myocarditis, and organ-specific disease associated with eosinophilia. In LOZARIL-related drug-induced hypersensitivity syndrome, discontinue LOZARIL immediately.

In a case of eosinophilia unrelated to LOZARIL identified (e.g., asthma, allergy, collagen vascular disease, parasitic infection, and peripheral plasmacytoma), the underlying cause and continue LOZARIL. C

Clozapine-related osophagia has also occurred with absence of organ involvement and cardiovascular without treatment. There are reports of successful challenge after discontinuation of clozapine, without recurrence of osophagia. In the absence of organ involvement, continue CL ZARIL under careful monitoring. If the total osophagia continues to crasovascular weeks with absence of symptoms as such, then discontinue treatment CL ZARIL through a challenge after the osophagia continues to cras should be based on the overall clinical assessment, consultation with a gastroenterologist.

5.8 QT Interval Prolongation

QT prolongation, Torsades de Pointes and other life-threatening ventricular arrhythmias, cardiac arrest, and sudden death have occurred with CL ZARIL treatment. When prescribed CL ZARIL, consider the risk of additional risk factors for QT prolongation and serious cardiovascular reactions. Consider that cras the risks include the following: history of QT prolongation, long QT syndrome family history of long QT syndrome or sudden cardiac death, significant cardiac arrhythmias, recent myocardial infarction, uncompensated heart failure, treatment with other medications that cause QT prolongation, treatment with medications that inhibit the metabolism of clozapine, and electrolyte abnormalities.

Prior to starting treatment with CL ZARIL, perform a careful physical examination, medical history, and concomitant medication history. Consider obtaining a baseline ECG and serum chemistry panel. Correct electrolyte abnormalities. Discontinue CL ZARIL if the QTc interval exceeds 500 msec. If at its maximum symptoms consistent with Torsades de Pointes or other arrhythmias, (e.g., syncope, respiratory distress, or alterations), obtain a cardiac evaluation and discontinue CL ZARIL.

Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of CL ZARIL. Drugs that cause QT prolongation include: selective psychotropics (e.g., ziprasidone, lurasidone, chlorpromazine, thioridazine, meprobamate, droperidol, meprobamate), selective antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sarafloxacin), Class IA antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalolol), and others (e.g., tamoxifen, levomephentermine, mephentermine, halofentanyl, meprobamate, dolasetron mesylate, robuscol or tacrolimus). Clozapine is primarily metabolized by CYP3A4, CYP2D6, and CYP1A2. Concomitant treatment with inhibitors of these enzymes may increase the concentration of CL ZARIL [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

Hyperkalemia and hypomagnesemia are the risks of QT prolongation. Hyperkalemia can result from duration of therapy, diarrhea, and other causes. Use caution when treating patients at risk for significant electrolyte disturbance, particularly hypokalemia. Obtain baseline measurements of serum potassium and magnesium levels, and periodically monitor electrolytes. Correct electrolyte abnormalities before starting treatment with CL ZARIL. O

5.9 Metabolic Changes

Atypical antipsychotic drugs, including CLOZARIL have been associated with metabolic changes that can increase cardiovascular and cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including CLOZARIL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on CLOZARIL should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In a pooled data analysis of 8 studies in adult subjects with schizophrenia, the mean changes in fasting glucose concentration in the CLOZARIL and chlorpromazine groups were +11 mg/dL and +4 mg/dL respectively. A higher proportion of the CLOZARIL group demonstrated categorical increases from baseline in fasting glucose concentrations, compared to the chlorpromazine group (Table 4). The CLOZARIL doses were 100-900 mg per day (mean modal dose: 512 mg per day). The maximum chlorpromazine dose was 1800 mg per day (mean modal dose: 1029 mg per day). The median duration of exposure was 42 days for CLOZARIL and chlorpromazine.

Table 6. Laboratory Changes in Fasting Glucose Level in Studies in Adult Subjects with Schizophrenia

Laboratory Parameter	Laboratory Change (at least once) from baseline	Treatment Arm	N	n (%)
Fasting Glucose	Normal (< 100 mg/dL) to High (> 126 mg/dL)	CLOZARIL	198	53 (27)
		Chlorpromazine	135	14 (10)
	Borderline (100 to 125 mg/dL) to High (≥ 126 mg/dL)	CLOZARIL	57	24 (42)
		Chlorpromazine	43	12 (28)

Dyslipidemia

Undesirable alterations in lipids have occurred in patients treated with atypical antipsychotics, including CLOZARIL. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using CLOZARIL, is recommended.

In a pooled data analysis of 10 studies in adult subjects with schizophrenia, CLOZARIL treatment was associated with increases in serum total cholesterol. No data were collected on LDL and HDL cholesterol. The mean increase in total cholesterol was 13 mg/dL in the CLOZARIL group and 15 mg/dL in the chlorpromazine group. In a pooled data analysis of 2 studies in adult subjects with schizophrenia, CLOZARIL treatment was associated with increases in fasting serum triglyceride. The mean increase in fasting triglyceride was 71 mg/dL (54%) in the CLOZARIL group and 39 mg/dL (35%) in the chlorpromazine group (Table 5). In addition, CLOZARIL treatment was associated with categorical increases in serum total cholesterol and triglyceride, as illustrated in Table 6. The proportion of patients with categorical increases in total cholesterol or fasting triglyceride increased with the duration of exposure. The median duration of CLOZARIL and chlorpromazine exposure was 45 days and 38 days, respectively. The CLOZARIL dose range was 100 mg to 900 mg daily; the maximum chlorpromazine dose was 1800 mg daily.

Table Me a ha ges i Total holesterol a d Triglyceride o ce ratio i Studies i Adult Subjects with Schizophre ia

Treatme t Arm	asele total cholesterol co ce ratio (mg/dL)	ha ge from baseli e mg/dL (%)
CLOZAPINE (N=334) B	184 B	+13 (7)
Chlorpromazine (N=333) B	18BB	+1BB(B)B
	asele total cholesterol co ce ratio (mg/dL)	ha ge from baseli e mg/dL (%)
CLOZAPINE (N=6) B	130B	+71 (64)B
Chlorpromazine (N=7) B	110B	+3BB(B)B

Table B at g o r a ha ge s i l i p o e B r a t i o i B t u b u s a d i s s o l u t i o n w i t h B r a n z i n e B

Laboratory Parameter	ategory ha ge (at least o ce) from baseli e B	Treatme t Arm	N B	(%)	
ToxB Ch (ra or B fast)	Increase by 20 mg/dL	CLOZAPINE	33BB	11B(B)B	
		Chlorpromazine	18BB	46(B)B	
	None (< 20 mg/dL) to B	CLOZAPINE	22B	18(B)B	
		Chlorpromazine	13BB	3 (B)B	
	Both (20-40 mg/dL) High	CLOZAPINE	79BB	30(B)B	
		Chlorpromazine	34B	14(B)B	
	Triglyceride (fasting)	Increase by 30 mg/dL	CLOZAPINE	6 B	3 (50)B
			Chlorpromazine	7 B	3 (B)B
None (< 30 mg/dL) to B		CLOZAPINE	4 B	0 (B)B	
		Chlorpromazine	6 B	2 (B)B	
Both (> 30 mg/dL and < 40 mg/dL) High		CLOZAPINE	1	1 (B)B	
		Chlorpromazine	1 B	0 (B)B	

Weight/B

Weight gain occurred with the therapeutic, including CLOZARIL. The weight gain was similar to that observed with CLOZARIL. Table 7 summarizes the weight gain by duration of exposure pooled from 11 studies with CLOZARIL and active comparators. The median duration of exposure was 609, 728, and 422 days, for CLOZARIL, olanzapine, and chlorpromazine, respectively. Mean

Table 7. Mean Change in Body Weight (kg) by Treatment Population in Studies in Adult Subjects

Metalloprotein	Exposure (Dy)	CLOZARIL (N=669)		Olanzapine (N=442)		Chlorpromazine (N=155)	
		n	Mean	n	Mean	n	Mean
Weight change from baseline	2 week (Dy 11-17)	6	+0.5	3	+0.5	2	-0.5
	4 week (Dy 21-35)	23	+0.7	8	+0.8	17	+0.6
	8 week (Dy 49-63)	12	+1.9	13	+1.8	16	+0.5
	12 week (Dy 70-84)	17	+2.9	5	+3.1	0	0
	24 week (Dy 154-178)	42	-0.0	12	+5.0	0	0
	48 week (Dy 302-350)	3	+3.0	3	+1.0	0	0

The mean weight gain led from 11 studies in adult subjects with CLOZARIL, olanzapine, and chlorpromazine. The median duration of exposure was 609, 728, and 422 days, for CLOZARIL, olanzapine, and chlorpromazine, respectively.

Table 8. Proportion of Adult Subjects in Studies in Weight Gain Related to Baseline

Weight change	CLOZARIL	Olanzapine	Chlorpromazine
n	669	44	15
≥ 7% (increased)	236 (35.3%)	20 (45.5%)	13 (87%)

5. Neuroleptic Weight Gain Syndrome

A multiplex neuroleptic weight gain syndrome (NWS) is a clinical entity characterized by the presence of a neuroleptic weight gain syndrome (NWS). The clinical features of NWS include a weight gain of at least 7% of the initial body weight, a weight gain of at least 10% of the initial body weight, a weight gain of at least 15% of the initial body weight, a weight gain of at least 20% of the initial body weight, and a weight gain of at least 25% of the initial body weight. The clinical features of NWS include a weight gain of at least 7% of the initial body weight, a weight gain of at least 10% of the initial body weight, a weight gain of at least 15% of the initial body weight, a weight gain of at least 20% of the initial body weight, and a weight gain of at least 25% of the initial body weight.

The clinical evaluation is consistent with this drug mechanism. It is important to consider the presence of other neuroleptic drugs (e.g., neuroleptic malignant syndrome, infection, heat stroke, primary CNS pathology, central cholinergic toxicity, extrapyramidal symptoms and drug fever).

The management of NMS should include (1) immediate discontinuation of neuroleptic drug therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of concomitant medical conditions. There is no evidence of relapse but specific pharmacologic treatment for NMS.

If patients require neuroleptic drug treatment after recovery from NMS, the potential for re-occurrence of neuroleptic drug therapy should be carefully considered. NMS can recur. Monitor closely if retreatment with neuroleptic.

NMS has occurred with CLOZARIL monotherapy and with concomitant CNS-active medication, including lithium.

5.11 Fever

During clozapine therapy, patients have experienced transient, clozapine-related fever. The peak incidence is within the first 3 weeks of treatment. While this fever is generally self-limited, it may necessitate discontinuation of treatment. The fever can be associated with a decrease in WBC count. Carefully evaluate patients with fever to rule out neuroleptic malignant syndrome. Consider the possibility of NMS [see Warnings and Precautions (5.10)].

5.12 Pulmonary Embolism

Pulmonary embolism and deep-vein thrombosis have occurred in patients treated with CLOZARIL. Consider the possibility of pulmonary embolism in patients who present with deep-vein thrombosis, chest pain, or with other respiratory symptoms. Whether pulmonary embolism and deep-vein thrombosis can be attributed to clozapine remains controversial.

5.13 Anticholinergic Toxicity

CLOZARIL has anticholinergic effects. Treatment with CLOZARIL can result in CNS and peripheral cholinergic toxicity. Use with caution in the presence of anticholinergic toxicity, paralytic ileus, urinary retention, or other conditions in which anticholinergic effects could be detrimental.

Treatment with CLOZARIL can result in tritention, including constipation, ileus, fecal impaction, and paralytic ileus. Urinary retention can be fatal. Constipation should be initiated by enemas or other laxatives. Caution with tritention with other anticholinergic agents.

5.14 Interference with Cognitive and Motor Performance

CLOZAPINE use should be avoided in patients with impaired motor performance. Caution should be exercised about operating hazardous machinery until they are reasonably certain that CLOZAPINE does not affect them adversely. These reactions may be dose-related. Consider reducing the dose if they occur.

5.15 Tardive Dyskinesia

Tardive dyskinesia (TD) has occurred in patients treated with typical drugs including CLOZAPINE. The syndrome consists of potentially irreversible, involuntary, dyskinetic movements. The risk of TD and the likelihood that it will become irreversible, are believed to increase with greater durations of treatment and higher total cumulative doses. However, the syndrome may develop after relatively brief treatment periods at low doses. Prescribe CLOZAPINE in a manner that is most likely to minimize the risk of developing TD. Use the lowest effective dose and the shortest duration necessary to control symptoms. Periodically assess the need for continued treatment. Consider discontinuing treatment if TD occurs. However, some patients may require treatment with CLOZAPINE despite the presence of the syndrome.

There is no known treatment for TD. However, the syndrome may remit partially or completely if treatment is discontinued. A typical treatment itself may suppress (or partially suppress) the signs and symptoms and it has the potential to mask the underlying process. The effect of symptom suppression on the long-term course of TD is unknown.

5.16 Cerebrovascular Adverse Reactions

Controlled trials in elderly patients with dementia-related psychosis treated with some typical antipsychotics have demonstrated an increased risk (compared to placebo) of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) including fatalities. The mechanism for this increased risk is not known. An increased risk cannot be excluded for CLOZAPINE or other antipsychotics or other patient populations. CLOZAPINE should be used with caution in patients with risk factors for cerebrovascular adverse reactions.

5.17 Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation of CLOZAPINE

Abrupt discontinuation of CLOZAPINE is essential (because of severe neutropenia or other medical conditions for example) [see *Dosage and Administration (2.4), Warnings and Precautions (5.1)*] monitor carefully for the recurrence of psychotic symptoms and adverse reactions related to cholinergic rebound such as profuse sweating, headache, use vomiting and diarrhea.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the label:

- Severe Neutropenia [see *Warnings and Precautions (5.1)*].

- Orthostatic Hypotension, Bradyarrhythmia, and Syncope [see Warnings and Precautions (5.3)].
- Seizure [see Warnings and Precautions (5.4)].
- Myocardial and Cardiac Conduction Abnormalities [see Warnings and Precautions (5.5)].
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Warnings and Precautions (5.6)].
- Encephalopathy [see Warnings and Precautions (5.7)].
- QT Interval Prolongation [see Warnings and Precautions (5.8)].
- Metabolic Change (Hyperglycemia and Diabetic Mellitus, Dyslipidemia, and Weight Gain) [see Warnings and Precautions (5.9)].
- Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.10)].
- Fever [see Warnings and Precautions (5.11)].
- Pulmonary Embolism [see Warnings and Precautions (5.12)].
- Antihypertensive Toxicity [see Warnings and Precautions (5.13)].
- Interference with Contraceptive and Motor Performance [see Warnings and Precautions (5.14)].
- Toxic Dyskinesia [see Warnings and Precautions (5.15)].
- Cerebral Vascular Adverse Reaction [see Warnings and Precautions (5.16)].
- Reversible Psychosis and Cholinergic Rebound after Abrupt Discontinuation [see Warnings and Precautions (5.17)].

6.1 Clinical Trials Experience

Because of the limited number of patients under evaluation, the following adverse reactions were observed in the limited trial of drug treatment compared to the limited trial of the other drug and may not reflect the rate observed in the large trial.

The most commonly reported adverse reactions ($\geq 5\%$) for CLOZARIL in the limited trial were: CNS reaction, including dizziness, headache, and tremor; cardiovascular reaction, including tachycardia, hypotension, and syncope; uterine muscle spasm; nervous system reaction, including hyperreflexia, weight gain, dry mouth, and visual disturbance; gastrointestinal reaction, including constipation and nausea; and fever. Table 9 summarizes the most commonly reported adverse reactions ($\geq 5\%$) in the CLOZARIL-treated patient (compared to the chlorpromazine-treated patient) in the pivotal 6-week, randomized trial in treatment-resistant schizophrenia.

Table 9. Common Adverse Reactions ($\geq 5\%$) in the 6-Week, Randomized, Chlorpromazine-controlled Trial in Treatment-Resistant Schizophrenia

Adverse Reaction	CLOZARIL (N = 126)(%)	Chlorpromazine (N = 142) (%)
Sedation	21	13
Tachycardia ^d	17 ^d	11

Constipation ⁴	16	12
Diarrhea	1	16
Hypotension	13	38
Fever (hyperthermia)	13	
Hypersensitivity	13	1
Hypertension	12	5
Headache	10	10
Nausea/vomiting	10	12
Dry mouth	5	20

Table 10 summarizes the adverse reactions reported in CLOZARIL-treated patients at a frequency of 2% or greater across all CLOZARIL studies (excluding the 2-year InterSePT™ Study). These rates are not adjusted for duration of exposure.

Table 10. Adverse Reactions (≥ 2%) Reported in CLOZARIL-treated Patients (N=842) across All CLOZARIL Studies (excluding the 2-year InterSePT™ Study)

Body System Adverse Reaction*	CLOZARIL N = 842 Percentage of Patients
Central Nervous System⁴	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope ⁴	6
Disturbed Sleep/Nightmares	
Restlessness	
Hypokinesia/Akinesia	
Agitation	
Seizures (convulsions) ⁴	3†
Rigidity	3
Akathisia	3
Confusion ⁴	3
Fatigue	2
Insomnia	2
Cardiovascular⁴	
Tachycardia	25†
Hypotension	9
Hypertension	4
Gastrointestinal	
Constipation	1
Nausea	5
Abdominal Discomfort/Heartburn ⁴	

Body System	CLOZARIL N = 842
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Urinary incontinence	2
Upper respiratory tract infection	
Salivary hypersecretion	31
Swallowing difficulty	6
Dry mouth	6
Vision blurred	5
Skin rash	
Rash	2
Headache	
Leukopenia	3
Mild to moderate weight gain	
Fatigue	5
Weight gain	4

† Rates are based on population exposed to either CLOZARIL or olanzapine in the clinical trial.

Table 10 summarizes the most commonly reported adverse events (10% of patients on CLOZARIL or olanzapine group) in the INTERCEPT™ Study. This was an adequate and well-controlled two-year study evaluating the efficacy of CLOZARIL relative to olanzapine in reducing the risk of suicidal behavior in patients with schizophrenia or schizoaffective disorder. The rates are not adjusted for duration of exposure.

Table 11. Incidence of Adverse Reaction in Active Treatment with CLOZARIL or Olanzapine in the INTERCEPT™ Study (≥10% in the CLOZARIL or olanzapine group)

Adverse Reaction	CLOZARIL N = 479 % Reporting	Olanzapine N = 477 % Reporting
Salivary hypersecretion	48%	6%
Somnolence	46%	25%
Weight increased	31%	56%
Dizziness (excluding vertigo)	27%	12%
Constipation	25%	10%
Insomnia	20%	33%
Nausea	17%	10%
Vomiting	17%	9%
Dyspepsia	14%	8%

Dystonia

Side effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of clozapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Central Nervous System

Delirium, EEG abnormality, myoclonus, paresthesia, possible cataplexy, status epilepticus, obsessive compulsive symptoms, and post-discontinuation cholinergic rebound adverse reactions.

Cardiovascular System

Atrial or ventricular fibrillation, ventricular tachycardia, QT interval prolongation, Torsades de Pointes, myocardial infarction, cardiac arrest, and periorbital edema.

Endocrine System

Pseudophochromocytoma.

Gastrointestinal System

Acute pancreatitis, dysphagia, sialorrhea and sweating.

Hepatology System

Cholestasis, hepatitis, jaundice, hepatotoxicity, hepatic steatosis, hepatic necrosis, hepatic fibrosis, hepatic cirrhosis, liver injury (hepatic, cholestatic, and mixed), and liver failure.

Immune System Disorders

Angioedema, leukocytoclastic vasculitis. 1

Urogenital System

Acute interstitial nephritis, nocturnal enuresis, priapism, and renal failure.

Skin and Subcutaneous Tissue Disorders

Hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, skin pigmentations disorders, and Stevens-Johnson syndrome.

Musculoskeletal System and Connective Tissue Disorders

Myasthenic syndrome, rhabdomyolysis, and systemic lupus erythematosus.

Respiratory System

Aspiration, pleural effusion, pneumonia, lower respiratory tract infection.

Hematologic System

Mild, moderate, or severe leukopenia, agranulocytosis, granulocytopenia, WBC decreased, deep-vein thrombosis, elevated hemoglobin/hematocrit, erythrocyte sedimentation rate (ESR) increased, sepsis, thrombocytosis, and thrombocytopenia.

Vision Disorders

Narrow-angle glaucoma.

Miscellaneous

Creatine phosphokinase elevation, hyperuricemia, hyponatremia, and weight loss.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect CLOZARIL

Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP3A4, and CYP2D6. Use caution when administering CLOZARIL concomitantly with drugs that are inducers or inhibitors of these enzymes.

CYP1A2 Inhibitors

Concomitant use of CLOZARIL and CYP1A2 inhibitors can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the CLOZARIL dose to one-third of the original dose when CLOZARIL is co-administered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, rifenoxacin). The CLOZARIL dose should be increased to the original dose when co-administration of strong CYP1A2 inhibitors is discontinued [see Dosage and Administration (2.6), Clinical Pharmacology (12.3)].

Moderate or severe CYP1A2 inhibitors include oral contraceptives and caffeine. Monitor patients closely when CLOZARIL is coadministered with these inhibitors. Consider reducing the CLOZARIL dosage if necessary [see *Dosage and Administration* (2.6)].

CYP2D6 and CYP3A4 Inhibitors O

Concomitant use with CLOZARIL and CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, propoxyphene, bupropion, fluoxetine, quinidine, duloxetine, terbinafine, or sertraline) can increase clozapine levels and lead to adverse reactions [see *Clinical Pharmacology* (12.3)]. Use caution and monitor patients closely when using such inhibitors. Consider reducing the CLOZARIL dose [see *Dosage and Administration* (2.6)].

CYP1A2 and CYP3A4 Inducers O

Concomitant use with drugs that induce CYP1A2 or CYP3A4 can decrease the plasma concentration of clozapine, resulting in decreased effectiveness of CLOZARIL. Tobacco smoke is a moderate inducer of CYP1A2. Strong CYP3A4 inducers include carbamazepine, phenytoin, St. John's wort, and rifampin. It may be necessary to increase the CLOZARIL dose if used concomitantly with inducers of these enzymes. However, concomitant use of CLOZARIL and strong CYP3A4 inducers is not recommended [see *Dosage and Administration* (2.6)].

Consider reducing the CLOZARIL dosage when discontinuing coadministered enzyme inducers; because discontinuation of inducers can result in increased clozapine plasma levels and an increased risk of adverse reactions [see *Dosage and Administration* (2.6)].

Drugs that Cause QT Interval Prolongation

Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of clozapine. Drugs that cause QT prolongation include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mioridazine, mesoridazine, droperidol, and pimozide), specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin), class IA antiarrhythmics (e.g., quinidine, procainamide) or class III antiarrhythmics (e.g., sotalolol), and others (e.g., penmidate, levomephexolone, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or cyclosporin) [see *Warnings and Precautions* (5.8)]. O

7.2 Potential for CLOZARIL to Affect Other Drugs

Concomitant use of CLOZARIL with other drugs metabolized by CYP2D6 can increase levels of these CYP2D6 substrates. Use caution when administering CLOZARIL with other drugs that are metabolized by CYP2D6. It may be necessary to use lower doses of such drugs than usually prescribed. Such drugs include specific antidepressants, phenothiazines, carbamazepine, and Type I antiarrhythmics (e.g., propafenone, flecainide, and encainide).

8 USE IN SPECIFIC POPULATIONS O

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate or well-controlled studies of clozapine in pregnant women.

Reproduction studies have been performed in rats and rabbits at doses up to 0.4 and 0.9 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis. The studies revealed no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, CLOZARIL should be used during pregnancy only if clearly needed.

Clinical Considerations

Consider the risk of exacerbation of psychosis when discontinuing or changing treatment with antipsychotic medications during pregnancy and postpartum. Consider early screening for gestational diabetes for patients treated with antipsychotic medications [see *Warnings and Precautions (5.9)*]. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Monitor neonates for symptoms of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding difficulties. The severity of complications can vary from self-limited symptoms to some neonates requiring intensive care, nitrous support and prolonged hospitalization.

Animal Data

In embryofetal developmental studies, clozapine had no effects on maternal parameters, litter sizes, or fetal parameters when administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 0.4 and 0.9 times, respectively, the MRHD of 900 mg/day on a mg/m² body surface area basis.

In peri/postnatal developmental studies, pregnant female rats were administered clozapine over the last third of pregnancy and until day 21 postpartum. Observations were made on fetuses at birth and during the postnatal period; the offspring were allowed to reach sexual maturity and mated. Clozapine caused a decrease in maternal body weight but had no effects on litter size or body weights of either F1 or F2 generations at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

8.3 Nursing Mothers

CLOZARIL is present in human milk. Because of the potential for serious adverse reactions in nursing infants from CLOZARIL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Use

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients in clinical studies utilizing CLOZARIL to determine whether these over 65 years of age differ from younger subjects in their response to CLOZARIL.

Orthostatic hypotension and tachycardia can occur with CLOZARIL treatment [see *Boxed Warning and Warnings and Precautions (5.3)*]. Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Elderly patients may be particularly susceptible to the anticholinergic effects of CLOZARIL, such as urinary retention and constipation [see *Warnings and Precautions (5.13)*].

Carefully select CLOZARIL doses in elderly patients, taking into consideration their greater frequency of decreased hepatic, renal, or cardiac function, as well as their concomitant disease and other drug therapy. Clinical experience suggests that the prevalence of tardive dyskinesia appears to be highest among the elderly; especially elderly women [see *Warnings and Precautions (5.15)*].

8.6 Patients with Renal or Hepatic Impairment

Dose reduction may be necessary in patients with significant impairment of renal or hepatic function. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted [see *Dosage and Administration (2.7)*, *Clinical Pharmacology (12.3)*].

8.7 CYP2D6 Poor Metabolizers

Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted [see *Dosage and Administration (2.7)*, *Clinical Pharmacology (12.3)*].

8.8 Hospice Patients

For hospitalized patients (i.e., terminally ill patients with a statistically significant proportion of six months or less), the risk of bleeding with ANC monitoring frequency to once every 6 months, fits the usual with the patient and his/her risk. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to manage other symptoms and the patient's terminal illness.

10 OVERDOSAGE

10.1 Overdosage Experience

The most commonly reported signs and symptoms associated with clozapine overdose are: sedation, dizziness, ataxia, hypotension, respiratory depression or failure; and hyperventilation. The reported signs and symptoms include: hypotension, and sinus tachycardia. Fatal overdoses have been reported with clozapine, usually at doses above 2500 mg. There have also been reports of patients recovering from overdoses within 48 hours.

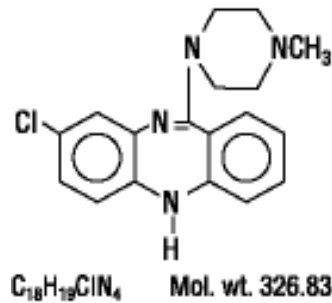
10.2 Management of Overdosage

For the most up-to-date information on the management of CLOZARIL overdose, contact your local Poison Control Center (1-800-222-1222). The toll-free number of your local Poison Control Center is listed in the *Physicians' Desk Reference*®, or standard trademark of PDR Network. Establish and maintain a nursing record of oxygenation and ventilation. Monitor and adjust vital signs. Use the usual symptomatology and supportive measures. There are no antidotes for CLOZARIL.

In massive overdoses, consider the possibility of multiple-drug involvement.

11 DESCRIPTION

CLOZARIL® (clozapine), a tricyclic antidepressant drug, is a dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenz[*b,e*] [1,4] diazepine. The structural formula is given below.



CLOZAPINE is available in the form of yellow tablets of 25 mg and 100 mg for oral administration.

Active ingredient: clozapine

Inert ingredients: colloidal silicon dioxide, lactose, magnesium stearate, polyethylene glycol (corn), and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine type 2 (D_2) and the serotonin type 2A ($5-HT_{2A}$) receptor. Clozapine also blocks histamine, cholinergic, and other dopaminergic and serotonergic receptors.

12.2 Pharmacodynamics

Clozapine demonstrates binding affinity to the following receptors: histamine H_1 (K_{11} 11 nM), adrenergic α_{1A} (K_{16} 16 nM), serotonin $5-HT_6$ (K_{4} 4 nM), serotonin $5-HT_{2A}$ (K_{54} 54 nM), muscarinic M_1 (K_{62} 62 nM), serotonin $5-HT_7$ (K_{63} 63 nM), serotonin $5-HT_{2C}$ (K_{94} 94 nM), dopamine D_4 (K_{24} 24 nM), adrenergic α_{2A} (K_{90} 90 nM), serotonin $5-HT_3$ (K_{95} 95 nM), serotonin $5-HT_{1A}$ (K_{120} 120 nM), dopamine D_2 (K_{160} 160 nM), dopamine D_1 (K_{270} 270 nM), dopamine D_5 (K_{454} 454 nM), and dopamine D_3 (K_{555} 555 nM).

Clozapine causes little or no prolactin elevation.

Clinical electroencephalogram (EEG) studies demonstrate that clozapine increases the delta and theta activity and decreases the alpha frequency. Enhanced synchronization occurs. Sleep architecture is not significantly affected. In a study of sleep, it was reported that the percentage of time spent in REM sleep was found to be increased to 85% of the total sleep time. In the event of a REM sleep, the onset of REM sleep occurred immediately after the end of sleep.

12.3 Pharmacokinetics

Absorption

In man, CLOZARIL tablets (25 mg and 100 mg) are equally bioavailable relative to a CLOZARIL solution. Following oral administration of CLOZARIL 100 mg twice daily, the average steady-state peak plasma concentration was 319 ng/mL (range: 102 to 771 ng/mL), occurring at the average of 2.5 hours (range: 1 to 6 hours) after dosing. The average trough concentration at steady state was 122 ng/mL (range: 41 to 343 ng/mL) after 100 mg twice daily dosing. Food does not appear to affect the systemic bioavailability of CLOZARIL. Thus, CLOZARIL may be administered with or without food.

Distribution

Clozapine is approximately 97% bound to serum proteins. The interaction between clozapine and other highly protein-bound drugs has not been fully evaluated but may be important [see Drug Interactions (7)].

Metabolism and Excretion

Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. Clozapine is a substrate for many cytochrome P450 isozymes in particular CYP1A2, CYP2D6, and CYP3A4.

Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The desmethylated, hydroxylated, and *N*-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite (norclozapine) to have only limited activity, while the hydroxylated and *N*-oxide derivatives were inactive. The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4 to 12 hours), compared to a mean elimination half-life of 12 hours (range: 4-66 hours), after achieving steady state with 100 mg twice daily dosing.

A comparison of single-dose and multiple-dose administration of clozapine demonstrated that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration-dependent pharmacokinetics. However, at steady state, approximately dose-proportional changes with respect to AUC (area under the curve), peak, and trough clozapine plasma concentrations were observed after administration of 37.5, 75, and 150 mg twice daily.

Drug-Drug Interaction Studies

Fluvoxamine

A pharmacokinetic study was conducted in 16 schizophrenic patients who received clozapine under steady-state conditions. After coadministration of fluvoxamine for 14 days, mean trough concentrations of clozapine and its metabolites, *N*-desmethylclozapine and clozapine *N*-oxide, were elevated about three-fold compared to baseline steady state concentrations. Mean

Paroxetine, Fluoxetine, and Sertraline

In a study of schizophrenic patients ($n=14$) who received clozapine under steady-state conditions, coadministration of paroxetine produced only minor changes in levels of clozapine and its metabolites. However, other published reports describe modest increases (1.5-fold) of clozapine and its metabolites in patients who received paroxetine, fluoxetine, or sertraline.

Specific Population Studies

Renal or Hepatic Impairment

No specific pharmacokinetic studies were conducted to evaluate the effects of renal or hepatic impairment on the pharmacokinetics of clozapine. Higher clozapine plasma concentrations are likely present in subjects with significant renal or hepatic impairment than in subjects with normal renal function.

CYP2D6 Poor Metabolizers

Approximately 3%–10% of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine at the given usual dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenic potential was demonstrated in long-term studies in mice at doses up to 0.3 mg/kg and 0.4 mg/kg, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface basis.

Mutagenesis

Clozapine was not genotoxic in the following studies: chromosomal aberrations: bacterial Ames test; *in vitro* mammalian V79 Chinese hamster cells; *in vitro* unscheduled DNA synthesis; sister chromatid exchange; *in vivo* micronucleus assay; mice.

Impairment of Fertility

Clozapine had no effect on any parameters of fertility in male rats given oral doses up to 0.4 mg/kg (the MRHD of 900 mg/day on a mg/m² body surface basis) for 14 days before mating and for 14 days before mating.

14 CLINICAL TRIALS

14.1 Treatment-Resistant Schizophrenia

The efficacy of CLOZARIL in treatment-resistant schizophrenia was established in a multicenter, randomized, double-blind, active-controlled (clopromazine) study in patients with a DSM-III diagnosis of schizophrenia who had inadequate responses to at least 3 different antipsychotics (from at least 2 different chemical classes) during the preceding 5 years. The antipsychotic trials must have been judged adequate; the antipsychotic dosages must have been equivalent to or greater than 1000 mg per day of clopromazine for a period of at least 6 weeks, each without significant reduction of the symptoms. There must have been no period of good functioning within the preceding 5 years. Patients must have had a baseline score of at least 45 on the investigator-rated Brief Psychiatric Rating Scale (BPRS). On the 18-item BPRS, 1 indicates the absence of symptoms, and 7 indicates severe symptoms; the maximum potential total BPRS score is 126. At baseline, the mean BPRS score was 61. In addition, patients must have had a score of at least 4 on at least two of the following four individual BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content. Patients must have had a Clinical Global Impressions – Severity Scale score of at least 4 (moderately ill).

In the prospective, lead-in phase of the trial, all patients (N=305) initially received single-blind treatment with aripiprazole (the mean dose was 61 mg per day) for 6 weeks. More than 80% of patients completed the 6-week trial. Patients with an inadequate response to aripiprazole (n=268) were randomized to double-blind treatment with CLOZARIL (N=126) or clopromazine (N=142). The maximum daily CLOZARIL dose was 900 mg; the mean daily dose was > 600 mg. The maximum daily clopromazine dose was 1800 mg; the mean daily dose was > 1200 mg.

The primary endpoint was treatment response, predefined as a decrease in BPRS score of at least 20% and either (1) a CGI-S score of ≤ 3 (mildly ill), or (2) a BPRS score of ≤ 35 , at the end of 6 weeks of treatment. Approximately 88% of patients from the CLOZARIL and clopromazine groups completed the 6-week trial. At the end of six weeks, 30% of the CLOZARIL group responded to treatment, and 4% of the clopromazine group responded to treatment. The difference was statistically significant ($p < 0.001$). The mean change in total BPRS score was -16 and -5 in the CLOZARIL and clopromazine group, respectively; the mean change in the 4 key BPRS item scores was -5 and -2 in the CLOZARIL and clopromazine group, respectively; and the mean change in CGI-S score was -1.2 and -0.4, in the CLOZARIL and clopromazine group, respectively. These changes in the CLOZARIL group were statistically significantly greater than in the clopromazine group ($p < 0.001$ in each analysis).

14.2 Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder

The effectiveness of CLOZARIL in reducing the risk of recurrent suicidal behavior was assessed in the International Suicide Prevention Trial (InterSePT™, a trademark of Novartis Pharmaceuticals Corporation). This was a prospective, randomized, open-label, active-controlled, multicenter, international, parallel-group comparison of CLOZARIL

versus placebo (Zyprexa[®], registered trademark of Eli Lilly and Company) in 56 patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for recurrent suicidal behavior. Only about one-fourth of these patients (27%) were considered resistant to standard psychotropic drug treatment. Therefore, patients must have met one of the following criteria:

- They had attempted suicide within the three years prior to their baseline evaluation.
- They had been hospitalized to prevent suicide attempt within the three years prior to their baseline evaluation.
- They demonstrated moderate-to-severe suicidal ideation with depressive component within one week prior to their baseline evaluation.
- They demonstrated moderate-to-severe suicidal ideation complicated by command hallucinations or delusions within one week prior to their baseline evaluation.

Dosing regimens for each treatment group were determined by individual investigators and were individualized by patient. Dosing was flexible, with a dose range of 200–1000 mg/day for CLOZARIL and 5–20 mg/day for placebo. For the 56 patients who received CLOZARIL or placebo in this study, there was extensive use of concomitant psychotropic medications: 84% with antipsychotics, 65% with antidepressants, and 28% with mood stabilizers. There was significant greater use of concomitant psychotropic medications among the patients in the placebo group.

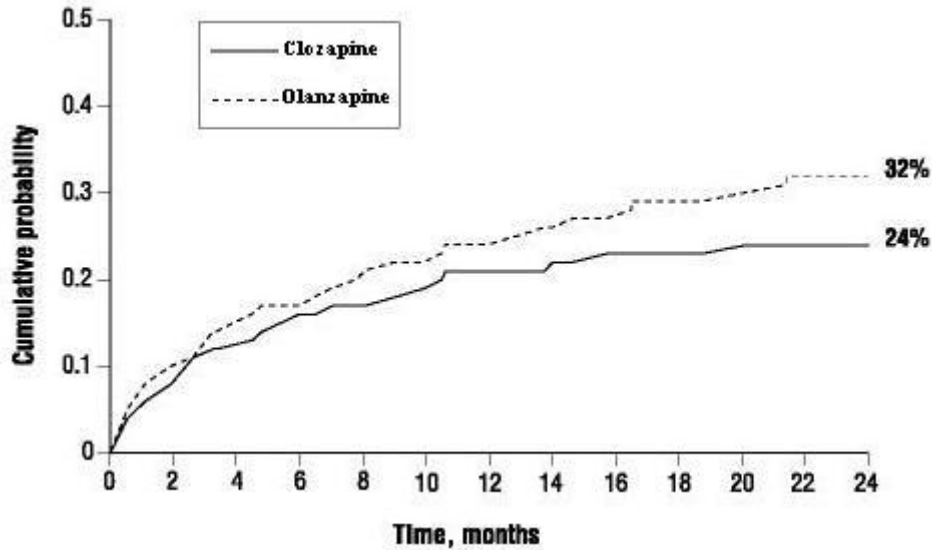
The primary efficacy measure was time to (1) significant suicide attempt, including completed suicide; (2) hospitalization due to imminent suicide risk, including suicide event; or (3) worsening of suicidal severity as demonstrated by “much worse” or “very much worse” from baseline on the Clinical Global Impressions Severity of Suicidal Thoughts scale assessed by the Brief Psychiatric Rating Scale (BPRS-SS-5.1) score. A determination of whether a reported event met criteria 1 or 2 was made by the Suicide Monitoring Board (SMB), a group of experts blinded to patient treatment.

All of the 80 patients were randomized to the study and 56 received study medication. 9 Sixty-two percent of the patients were diagnosed with schizophrenia, and the remainder (38%) were diagnosed with schizoaffective disorder. Only about one-fourth of the total patient population (27%) was identified as “treatment-resistant” to baseline. There were more men than women in the study (61% of patients were male). The mean age of patients entering the study was 37 years of age (range 18–60). Most patients were Caucasian (71%), 15% were Black, 1% were Asian, and 13% were classified as being of “other” races.

Patients treated with CLOZARIL had statistically significantly longer delay to the time to recurrent suicidal behavior or risk compared with placebo. This result should be interpreted as evidence of the effectiveness of CLOZARIL in delaying time to recurrent suicidal behavior and demonstrating the superiority of CLOZARIL versus placebo. 9

The probability of experiencing (1) a significant suicide attempt, including completed suicide, or (2) hospitalization because of imminent suicide risk, including increased effectiveness for suicide frequency for patients receiving hospitalized, was lower for CLOZARIL v patients than for olanzapine patients at Week 104: CLOZARIL 24% versus olanzapine 32%; 95% CI of the difference: 2%, 14% (Figure 1).

Figure 1. Cumulative Probability of a Significant Suicide Attempt or Hospitalization to Prevent Suicide in Patients with Schizophrenia or Schizoaffective Disorder at v High Risk of Suicidality



16 HOW SUPPLIED/STORAGE AND HANDLING v

16.1 How Supplied

CLOZARIL® (clozapine) is available in 25 mg and 100 mg round, peach-colored, uncoated tablets with faceted score lines.

CLOZARIL® (clozapine) Tablets v

25 mg

Engraved with “CLOZARIL” near the periphery of the tablet.

Engraved with faceted score and “25” near the other side. v

Bottle of 100 NDC 0078-0126-05

Bottle of 500 NDC 0078-0126-08

Unit d ck g f 100: 2 x 5 tri , 10 bli t r r tri .7..... NDC 00 8-0126-06
100 mg

Engr v d with “CLOZARIL” nc n th ri h ry f n id .

Engr v d with f cilit t d c r nd “100” nc n th th r id . 7

B ttl f 100 NDC 00 8-012 -05

B ttl f 500 .7..... NDC 00 8-012 -08

Unit d ck g f 100: 2 x 5 tri , 10 bli t r r tri .7..... NDC 00 8-012 -06

16.2 Storage and Handling

St r g t m p r tur h uld n t xc d 30°C (86°F).

K ut fr ch f childr n.

17 PATIENT COUNSELING INFORMATION

Di cu th f ll wing i u with ti nt nd c r giv r :

- Severe Neutropenia:

- In tract ti nt (nd c r giv r) b ginning tr tm ent with CLOZARIL b ut th ri k fd v l ing v r n utr ni nd inf cti n.
- In tract ti nt t immedi t ly r rt t th ir hy ici n ny ym pt m r ign f 7 inf cti n (.g., flu-lik illn ; f v r; l th rgy; g n r l w kn r m d i ; mucu m æbr n ulc r ti n; kin, h ryng l, v gin l, urin ry, r ulm æn ry inf cti n; r xtr mew kn r l th rgy) ccuring t ny tim eduring CLOZARIL th r y, t id in v lu ti n f r n utr ni nd t in titut r m pt nd r ri t m æ g m æt. [see Warnings and Precautions (5.1), (5.10), and (5.11)].
- Inf rm ti nt nd c r giv r CLOZARIL i v il bl nly thr ugh r trict d r gr m c ll d th Cl z in REMS Pr gr m d ign d t n ur th r quir d bl d m æit ring, in rd rt r duc th ri k fd v l ing v r n utr ni . Adv ti nt nd c r giv r f th imp r t nc fh ving bl d t t d f ll w :
 - W kly bl d t t r r quir d fr th fir t 6 m nth .
 - An ANC i r quir d v ry 2 w k fr th n xt 6 m nth if n cc t bl ANC i m ænt in d during th fir t 6 m nth fc ntinu u th r y,
 - An ANC i r quir d nc v ry 4 w k th r ft r if n cc t bl ANC i 7 m ænt in d during th c nd 6 m nth fc ntinu u th r y.

- CLOZOL is available only from certified pharmacies participating in the program. Provide patient (and caregiver) with website information and the telephone number on how to obtain the product.
- Orthostatic Hypotension, Bradycardia, and Syncope: Inform patient and caregiver about the risk of orthostatic hypotension and syncope, especially during the period of initial dose titration. Instruct them to strictly follow the clinician's instructions for dosage and administration. Advise patient to consult the clinician immediately if they feel faint, lose consciousness or have signs or symptoms suggestive of bradycardia or arrhythmia [see *Dosage and Administration (2.2) and Warnings and Precautions (5.3)*].
- Seizures: Inform patient and caregiver about the significant risk of seizure during CLOZOL treatment. Caution them about driving and any other potentially hazardous activity while taking CLOZOL [see *Warnings and Precautions (5.4)*]. P
- QT Interval Prolongation: Advise patient to consult the clinician immediately if they feel faint, lose consciousness or have signs or symptoms suggestive of arrhythmia. Instruct patient to not take CLOZOL with other drug that cause QT interval prolongation. Instruct patient to inform the clinician that they are taking CLOZOL before any new drug [see *Warnings and Precautions (5.8.) and Drug Interactions (7.1)*].
- Metabolic Changes (hyperglycemia and diabetes mellitus, dyslipidemia, weight gain): Educate patient and caregiver about the risk of metabolic change and the need for specific monitoring. The risks include hyperglycemia and diabetes mellitus, dyslipidemia, weight gain, and cardiovascular reaction. Educate patient and caregiver about the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus (e.g., polydipsia, polyuria, polyphagia, and weakness). Monitor all patient for the symptoms at least who are diagnosed with diabetes or have risk factor for diabetes (obesity, family history of diabetes) should have the fasting blood glucose monitored before beginning treatment and periodically during treatment. Patient who develop symptoms of hyperglycemia should have assessment of fasting glucose. Clinical monitoring of weight recommended [see *Warnings and Precautions (5.9)*]. P
- Interference with Cognitive and Motor Performance: Because CLOZOL may have the potential to impair judgment, thinking, or motor skills, patient should be cautioned about operating hazardous machinery, including automobile, until they are reasonably certain that CLOZOL therapy does not affect them adversely [see *Warnings and Precautions (5.14)*].
- Missed Doses and Re-initiating Treatment: Inform patient and caregiver that if the patient misses taking CLOZOL for more than 2 days, they should not restart the medication at the same dosage but should contact the physician for dosing instructions [see *Dosage and Administration (2.5) and Warnings and Precautions (5.1, 5.3)*].

- Pregnancy Patients and caregivers should notify the clinician if the patient becomes pregnant or intends to become pregnant during therapy. [see Use in Specific Populations (8.1)]
- Nursing Advise patients and caregivers that the patient should not breast feed an infant if they are taking CLOZARIL. [see Use in Specific Populations (8.3)]
- Concomitant Medication Advise patients to inform their health care provider if they are taking, or plan to take, any prescription or over-the-counter drugs; there is a potential for significant drug-drug interactions [see Dosage and Administration (2.6), Drug Interactions (7.1), and Table 1].

*Zyrex[®] (olanzapine) is a registered trademark of Eli Lilly and Company.

**Trademark of Thomson Healthcare, Inc.

CLOZARIL[®] is a registered trademark of Novartis Pharmaceuticals Corporation.

T2012-XX

September, 2015 p

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019758Orig1s061

REMS

RISK EVALUATION AND MITIGATION STRATEGY (REMS) /
SINGLE SHARED SYSTEM FOR CLOZAPINE

I. GOALS

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

- A. Educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements
- B. Informing patients about the risk of severe neutropenia and appropriate monitoring requirements
- C. Ensuring compliance with the monitoring schedule for absolute neutrophil count (ANC) prior to dispensing clozapine
- D. Ensuring the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the Prescribing Information
- E. Establishing long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry

II. REMS ELEMENTS

A. Elements To Assure Safe Use

- . Healthcare providers who prescribe clozapine are specially certified.
 - a. To become specially certified to prescribe clozapine in the Clozapine REMS Program, healthcare providers must:
 - i. Review the Prescribing Information for clozapine;
 - ii. Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and successfully complete the *Knowledge Assessment for Healthcare Providers*; and
 - iii. Enroll in the Clozapine REMS Program by completing the *Clozapine REMS Prescriber Enrollment Form*.

b. As a condition of certification, prescribers must

i. Enroll each patient in the Clozapine REMS Program by

- 1.) Informing the patient about the risks associated with clozapine including severe neutropenia and the Clozapine REMS Program requirements by using *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*, and providing it to the patient or caregiver unless clinical judgment indicates that the patient's adherence to the treatment regimen will be negatively impacted by providing *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*
- .) Completing the *Clozapine REMS Patient Enrollment Form* for each patient. Submit the completed form to the Clozapine REMS Program and store a copy in the patient's records.

ii. Perform the following requirements on an ongoing basis for each patient and report to the Clozapine REMS Program via the online system, by fax, or by calling the Clozapine REMS Program contact center

- 1.) Report ANC according to the monitoring schedule described in the Prescribing Information.
- .) Report authorization to continue treatment for patients with an ANC that falls below the acceptable range described in the Prescribing Information, when the prescriber determines the benefits exceed the risks of developing severe neutropenia.

c. Clozapine Sponsors must

- i. Ensure that healthcare providers who prescribe clozapine are specially certified in accordance with the requirements described above. :
- ii. Ensure that healthcare providers can complete the certification process, patient enrollment and management online or by fax to the Clozapine REMS Program.
- iii. Ensure that healthcare providers who prescribe clozapine are notified when they have been certified in the Clozapine REMS Program.
- iv. Maintain a validated, secure database of healthcare providers who are certified to prescribe clozapine in the Clozapine REMS Program. Clozapine Sponsors must ensure that the prescriber's REMS requirements are met and may de-certify noncompliant prescribers if

the requirements do not continue to be met.

- v. Maintain a validated, secure database of patients enrolled in the Clozapine REMS Program
- vi. Ensure that certified prescribers are provided access to the database of all certified pharmacies and enrolled patients.
- vii. Provide *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* to healthcare providers who:
 - 1.) attempt to prescribe clozapine and are not yet certified, or
 - 2.) inquire about how to become certified.
- viii. Ensure that within 30 calendar days of REMS approval, the REMS materials listed below are available on the Clozapine REMS Program website (www.clozapinerems.com), or by calling the Clozapine REMS Program contact center at 844-267-8678.

The following materials are part of the REMS and are appended:

- *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
- *Knowledge Assessment for Healthcare Providers*
- *Clozapine REMS Prescriber Enrollment Form*
- *Clozapine REMS Prescriber Designee Enrollment Form*
- *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*
- *Clozapine REMS Patient Enrollment Form*
- Clozapine REMS Program website

2. Pharmacies that dispense clozapine are specially certified.
 - a. To become specially certified to dispense clozapine in the Clozapine REMS Program, pharmacies must:
 - i. Designate an authorized representative to complete certification on behalf of the pharmacy using the appropriate form:
 - 1.) *Clozapine REMS Pharmacy Enrollment Form*
 - 2.) *Clozapine REMS Chain Headquarters Pharmacy Enrollment Form*
 - ii. Ensure the authorized representative will oversee implementation and compliance with the Clozapine REMS Program requirements by doing the following:
 - 1.) Review *Clozapine and the Risk of Neutropenia: A Guide for*

Healthcare Providers and successfully complete the Knowledge Assessment for Healthcare Providers.

- 2.) Ensure all relevant staff involved in the dispensing of clozapine are trained on the Clozapine REMS Program requirements as described in *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and maintain records of staff training.
 - a.) For pharmacies that have a pharmacy management system that supports electronic telecommunication verification, each pharmacist must be trained utilizing established training protocols for their certified pharmacy.
 - b.) For pharmacies that have a pharmacy management system that does NOT support electronic telecommunication verification, each pharmacist must be trained by reviewing *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and successfully completing the *Knowledge Assessment for Healthcare Providers*.
- iii. Put processes and procedures in place to ensure the following verifications and reporting requirements are completed:
 - 1.) Verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program prior to dispensing clozapine,
 - 2.) Verify the ANC is current (within 7 calendar days of the blood draw),
 - 3.) Verify the ANC is within the acceptable range described in the Prescribing Information or the prescriber has authorized the continuation of clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits exceed the risks of developing severe neutropenia prior to dispensing clozapine, and
 - .) Report dosing information for each clozapine prescription/fill to the Clozapine REMS Program
- iv. Maintain appropriate documentation that all processes and procedures are in place and are being followed for the Clozapine REMS Program and provide it upon request to the Clozapine Sponsors, FDA, or a third party.
- v. Comply with audits by the Clozapine Sponsors, FDA, or a third party to ensure that all processes and procedures are in place and are being followed for the Clozapine REMS Program.

b. As a condition of certification:

i. Outpatient pharmacies:

- 1.) that support electronic telecommunication verification with the Clozapine REMS Program system must:
 - a.) Ensure the pharmacy enables its pharmacy management system to support communication with the Clozapine REMS Program system using established telecommunication standards and runs the standardized validation test transaction(s) to validate the system enhancements.
 - b.) Dispense clozapine to patients only after obtaining a predispose authorization by processing a clozapine prescription, including cash claims, through their pharmacy management system to electronically:
 - (1) verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program.
 - (2) verify the ANC is current and within the acceptable range described in the Prescribing Information, or that the prescriber has authorized the continuation of clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits exceed the risks of developing severe neutropenia.
 - (3) report dosing information for each clozapine prescription/visit to the Clozapine REMS program.
- 2.) that do NOT support electronic telecommunication verification with the Clozapine REMS Program system must dispense clozapine to patients only after obtaining a predispose authorization by accessing the Clozapine REMS Program website or calling the Clozapine REMS Program contact center to:
 - a.) verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program.
 - b.) verify the ANC is current and within the acceptable range described in the Prescribing Information, or that the prescriber has authorized the continuation of clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the

benefits exceed the risks of developing severe neutropenia

- c.) report dosing information for each clozapine prescription/fill to the Clozapine REMS Program.
- ii. Inpatient pharmacies must:
 - 1.) Dispense clozapine to patients only after accessing the Clozapine REMS Program website or calling the Clozapine REMS Program contact center to verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program.
 - 2.) Dispense clozapine to patients only after accessing the Clozapine REMS Program website, calling the Clozapine REMS Program contact center or checking the patient's medical record to verify the ANC is current and within the acceptable range described in the Prescribing Information, or the prescriber has authorized the continuation of clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits exceed the risks of developing severe neutropenia.
- c. Clozapine Sponsors must:
 - i. Ensure that pharmacies that dispense clozapine are specially certified, in accordance with the requirements described above.
 - ii. Ensure that authorized representatives can complete the certification process and pharmacists can complete training online or by fax to the Clozapine REMS Program.
 - iii. Ensure that pharmacies are notified when they have been certified in the Clozapine REMS Program.
 - iv. Verify every 2 years that the authorized representative's name and contact information corresponds to that of the current designated authorized representative for the certified pharmacy. If different, require the pharmacy to re-certify with a new authorized representative.

The following materials are part of the REMS and are appended:

- *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
- *Knowledge Assessment for Healthcare Providers*
- *Clozapine REMS Pharmacy Enrollment Form*
- *Clozapine REMS Chain Headquarters Pharmacy Enrollment Form*
- Clozapine REMS Program Website

3. Clozapine will be dispensed with evidence or other documentation of safe-use conditions.
 - a. To enroll a patient in the Clozapine REMS Program, each prescriber must complete a *Clozapine REMS Patient Enrollment Form* indicating that the patient or their caregiver has:
 - i. Been provided *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers* unless clinical judgment indicates that the patient's adherence to the treatment regimen will be negatively impacted by providing *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*
 - ii. Been informed by the prescriber of the risks of clozapine and the Clozapine REMS Program requirements, using *What You Need To Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers*.
 - b. Clozapine Sponsors must:
 - i. Ensure that the certified prescriber is able to submit the completed *Clozapine REMS Patient Enrollment Form* online or by fax to the Clozapine REMS Program.
 - ii. Ensure that the certified pharmacy can verify that the prescriber is certified and each patient treated with clozapine is enrolled in the Clozapine REMS Program prior to dispensing (see Section II.A.2).

The following materials are part of the REMS and are appended:

- *Clozapine REMS Patient Enrollment Form*

4. Each patient using Clozapine is subject to certain monitoring.

Clozapine Sponsors must ensure that the certified pharmacy can verify the ANC is current and within the acceptable range described in the Prescribing Information, or that the prescriber has authorized the continuation of treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits exceed the risks of developing severe neutropenia prior to dispensing clozapine.
5. Each patient using clozapine is enrolled in a registry.
 - a. Clozapine Sponsors must ensure that certified prescribers enroll all patients in the Clozapine REMS Program using the *Clozapine REMS Patient Enrollment Form*.
 - b. Clozapine Sponsors must maintain a Clozapine REMS Program registry. The

primary objective of the Clozapine REMS Program registry is to ensure patient safety and safe use of clozapine through periodic monitoring for non-severe neutropenia.

- c. Clozapine Sponsors must ensure that patient enrollment can be completed via Clozapine REMS Program website or by fax.

B. Implementation System

1. Clozapine Sponsors must ensure that clozapine is only distributed to certified pharmacies by:
 - a. Ensuring the wholesalers/distributors who distribute clozapine comply with the program requirements for wholesalers/distributors. In order for a wholesaler/distributor to distribute clozapine, the wholesalers/distributors must:
 - i. Put processes and procedures in place to verify, prior to distributing clozapine, that the pharmacies are certified.
 - ii. Train all relevant staff on the Clozapine REMS Program requirements.
 - iii. Agree to be audited by the Clozapine Sponsors, FDA, or a third party to ensure that all processes and procedures are in place and are being followed for the Clozapine REMS Program.
 - iv. Maintain appropriate documentation and make it available for audits.
 - v. Provide distribution data to the individual Clozapine Sponsors.
 - b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of clozapine and provide the data to the individual Clozapine Sponsors.
 - c. Clozapine Sponsors must monitor distribution data and audit the wholesalers/distributors within one year after the wholesaler/distributor is enrolled to ensure that all processes and procedures are in place and functioning to support the requirements of the Clozapine REMS Program. Clozapine Sponsors must institute corrective action if non-compliance is identified.
2. Clozapine Sponsors must maintain a validated, secure database of pharmacies that are certified to dispense clozapine in the Clozapine REMS Program.
3. Clozapine Sponsors must maintain adequate records of clozapine distribution, dispensing, certified prescribers, pharmacies, distributors/wholesalers, and patients to meet the REMS requirements.

4. Clozapine Sponsors must ensure that pharmaceuticals' REMS requirements are met and may de-certify non-compliant pharmaceuticals if the requirements do not continue to be met.
5. Clozapine Sponsors must maintain a validated, secure database of patients who are enrolled in the Clozapine REMS Program.
6. Clozapine Sponsors must maintain a Clozapine REMS Program contact center to support prescribers and pharmaceuticals interfacing with the Clozapine REMS Program.
7. Clozapine Sponsors must ensure that all materials listed in or appended to the Clozapine REMS document are available through the Clozapine REMS Program website www.lozapinerems.com or by calling the Clozapine REMS Program contact center.
8. The Clozapine REMS Program website (www.lozapinerems.com) must continue for the duration of the REMS. The Clozapine REMS Program website must include the option to print versions of the Clozapine REMS Program materials. Individual, product-specific Clozapine websites for health care professionals must include a prominent REMS-specific link to the Clozapine REMS Program website.
 - Clozapine Sponsors must continuously monitor the certified pharmaceuticals to ensure the requirements of the Clozapine REMS Program are being met. Clozapine Sponsors must institute corrective action if non-compliance is identified.
10. Clozapine Sponsors must audit certified pharmaceuticals that have ordered Clozapine to ensure that all processes and procedures are in place and functioning to support the requirements of the Clozapine REMS Program on the following schedule:
 - a. Eight percent within one year from the date of initial approval of the REMS
 - b. Eight percent every two years thereafter

Clozapine Sponsors must institute corrective action if non-compliance is identified.

11. Clozapine Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Clozapine REMS Program based on monitoring and evaluation of the Clozapine REMS Program.

III. Timetable for Submission of Assessments

Clozapine NDA Sponsors must submit REMS Assessments to the FDA at 6 months and 12 months from the date of initial approval of the REMS [September 14, 2015], and then annually thereafter.

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should include no earlier than 60 calendar days before the submission date for that assessment. Clozapine

Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

Instructions

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

To submit this form via fax, please complete all required fields below and fax to 844-404-8876. You will receive a confirmation via the contact preference you list below.

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

1. Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
2. Successfully complete the *Knowledge Assessment for Healthcare Providers*
3. Complete and submit this one-time *Prescriber Enrollment Form* along with the completed *Knowledge Assessment for Healthcare Providers*

If you have any questions, require additional information, or need further copies of Clozapine REMS Program documents, please visit the program website at www.clozapinerems.com, or call the Clozapine REMS Program at 844-267-8678.

Prescriber Responsibilities

By signing this form, I attest that:

1. I understand that clozapine is only available through the Clozapine REMS Program and that I must comply with the program requirements to prescribe clozapine
2. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, reviewed the clozapine Prescribing Information, and successfully completed the *Knowledge Assessment for Healthcare Providers*
3. I understand the risk of severe neutropenia associated with clozapine
4. Prior to initiating treatment, I agree to provide *What You Need To Know About Clozapine: A Guide for Patients and Caregivers* to each patient and/or his/her caregiver. I will review it with him/her to inform them about the risks associated with clozapine, including severe neutropenia and the Clozapine REMS Program requirements – unless I determine that the patient's adherence to the treatment regimen will be negatively impacted by providing *What You Need To Know About Clozapine: A Guide for Patients and Caregivers*
5. I will enroll all patients I treat with a clozapine product in the Clozapine REMS Program
6. I understand the ANC testing and monitoring requirements as described in the clozapine Prescribing Information
7. I understand there is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
8. I will order ANC testing for each patient according to the clozapine Prescribing Information
9. I will report the ANC for each patient to the Clozapine REMS Program and I understand the ANC must be provided before clozapine can be dispensed
10. I understand that, as described in *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, I must authorize the continuation of clozapine treatment if the patient has moderate or severe neutropenia before clozapine can be dispensed
11. I agree that personnel from the Clozapine REMS Program may contact me to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
12. 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 Program
13. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

Prescriber Information (All Fields Required Unless Otherwise Indicated)

First Name:	MI (opt):	Last Name:
NPI:	DEA:	
Email:	Credentials (MD, DO, NP, PA):	
Clinic / Practice Name:		
Address:		
City:	State:	Zip Code:
Phone:	Ext (opt):	Fax:
Contact Preference (please select one): <input type="checkbox"/> Email <input type="checkbox"/> Fax		

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

Instructions

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

To submit this form via fax, please complete all required fields below and fax to 844-404-8876. You will receive a confirmation via the contact preference you list below.

Clozapine is only available through the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. In order to access the Clozapine Program as a prescriber's designee, you must complete this form.

If you have any questions, require additional information, or need further copies of Clozapine REMS Program documents, please visit the program website at www.clozapinerems.com, or call the Clozapine REMS Program at 844-267-8678.

Prescriber Designee Responsibilities

By signing this form, you acknowledge that you will act on behalf of the certified prescriber (identified below) to comply with the Clozapine REMS Program requirements.

I understand:

1. Clozapine is only available through the Clozapine REMS Program and that I must comply with the program requirements
2. There is a risk of severe neutropenia associated with clozapine
3. **For Outpatients:** An ANC must be reported to the Clozapine REMS Program for each patient, and I understand these results must be provided before clozapine can be dispensed
4. **For Inpatients:** An ANC must be reported to the Clozapine REMS Program for each patient within 7 days from the date of the blood draw
5. A certified prescriber must authorize the continuation of clozapine treatment, if the patient has moderate or severe neutropenia before clozapine can be dispensed to a patient
6. 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 Program
7. Personnel from the Clozapine REMS Program may contact me to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
8. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

Designee Information (All Fields Required)

First Name:		Last Name:	
Email:			
Phone:	Ext (opt):	Fax:	
Contact Preference (please select one): <input type="checkbox"/> Email <input type="checkbox"/> Fax			
Prescriber Designee Signature:			Date (MM/DD/YYYY):

Prescriber Information (All Fields Required)

First Name:		Last Name:	
REMS Certification ID (opt):	DEA:	NPI:	
Prescriber Signature:			Date (MM/DD/YYYY):

Instructions

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

To submit this form via fax, please complete all required fields below and fax to 844-404-8876. You will receive a confirmation via the contact preference you select below.

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

1. Select an authorized representative
2. Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
3. Successfully complete the *Knowledge Assessment for Healthcare Providers*
4. Complete and submit this one-time Clozapine REMS Chain Headquarters Pharmacy Enrollment Form along with the completed *Knowledge Assessment for Healthcare Providers*
5. Implement the necessary staff training and processes at both a headquarter level and at each dispensing location to comply with the Clozapine REMS Program requirements.

If you have any questions, require additional information, or need further copies of Clozapine REMS Program documents, please visit the program website at www.clozapinerems.com, or call the Clozapine REMS Program at 844-267-8678.

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to coordinate the activities of the Clozapine REMS Program. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, the Prescribing Information, and I understand:

1. Pharmacies must certify in the Clozapine REMS Program to order and dispense clozapine
2. The risk of severe neutropenia associated with clozapine and the importance of ANC monitoring
3. There is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
4. Clozapine manufacturers, their agents and contractors may contact me to obtain names of our pharmacists to contact them via phone, mail, or email to survey on the effectiveness of the program requirements for the Clozapine REMS Program

On behalf of the pharmacy, I agree to comply with the following program requirements:

5. My pharmacy will establish procedures and protocols that are subject to audit, to help ensure compliance with the requirements of the Clozapine REMS Program, including the following, before dispensing clozapine:
 - All pharmacists and relevant staff involved in dispensing clozapine are trained and a record of the training is maintained
 - Through electronic communication with the Clozapine REMS Program using established telecommunications standards, my pharmacy will dispense clozapine to each patient only after obtaining authorization by electronically verifying documentation of the following:
 - Prescriber is certified in the Clozapine REMS Program
 - Pharmacy is certified in the Clozapine REMS Program
 - Patient is enrolled in the Clozapine REMS Program
 - The ANC is current and acceptable or the prescriber has authorized continuing treatment if the ANC is abnormal
 - This information will be verified by processing all clozapine prescriptions, including cash claims, through the pharmacy management system
 - Fill and dispense no more than the amount of clozapine necessary to treat the patient until the next blood draw/ANC or as directed by the prescriber
6. My pharmacy agrees not to sell, loan, or transfer any clozapine inventory to any other pharmacy institution, distributor, or prescriber that is not enrolled in the Clozapine REMS Program, and will establish procedures and protocols to support these requirements that are subject to audit
7. Pharmacies will renew enrollment in the Clozapine REMS Program every two years to maintain certification to order and dispense clozapine
8. Pharmacies will make documentation available to the clozapine manufacturers and/or a designated third party or the FDA to verify understanding of, and adherence to, the requirements of the Clozapine REMS Program
9. Clozapine REMS Program personnel may contact pharmacists in my pharmacies to gather information, resolve discrepancies, or to provide other information related to the Clozapine REMS Program
10. For each trained dispensing location provide the following information (Pharmacy Name, NCPDP or NPI or DEA, Address, Phone, Fax, Email, Store Number, and Responsible Pharmacist name)
11. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

Chain Headquarters Pharmacy Information (All Fields Required)

Name:		
Chain ID:		
Address:		
City:	State:	Zip Code:
Phone:	Fax:	

Authorized Representative Information (All Fields Required)

First Name:		Last Name:	
Credentials:	<input type="checkbox"/> R.Ph	<input type="checkbox"/> PharmD	<input type="checkbox"/> BCPS <input type="checkbox"/> Other
Phone:	Fax:	Email:	
Contact Preference (please select one): <input type="checkbox"/> Email <input type="checkbox"/> Fax			
Authorized Representative Signature:			Date (MM/DD/YYYY):

Next Steps

1. Once this form is processed, you will receive instructions on submitting test transaction(s) to the Clozapine REMS Program to ensure that your pharmacy management system has been successfully configured/updated to communicate with the Clozapine REMS Program
2. After successful completion of the test transactions, you will receive a pharmacy certification confirmation. Upon receipt, your corporate pharmacy is certified and your dispensing locations are now eligible to complete their training
3. Once each dispensing location is trained, it is your responsibility to report documentation of training to the Clozapine REMS Program online through www.clozapinerems.com, or by contacting the Clozapine REMS Program Contact Center to obtain instructions on providing a list of certified pharmacy locations. Once the Clozapine REMS Program confirms the required dispensing location information, this dispensing location will be certified and permitted to purchase, receive, and dispense clozapine

Instructions

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

To submit this form via fax, please complete all required fields below and fax to 844-404-8876. You will receive a confirmation via the contact preference you list below.

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 Risk Evaluation and Mitigation Strategy (REMS) Program. 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 Healthcare Providers*
2. Successfully complete the *Knowledge Assessment for Healthcare Providers*
3. Complete and submit this one-time *Clozapine REMS Pharmacy Enrollment Form* along with the completed *Knowledge Assessment for Healthcare Providers*
4. Implement the necessary staff training and processes to comply with the Clozapine REMS Program requirements

If you have any questions, require additional information, or need further copies of Clozapine REMS Program documents, please visit the program website at www.clozapinerems.com, or call the Clozapine REMS Program at 844-267-8678.

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to coordinate the activities of the Clozapine REMS Program. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and the Prescribing Information and I understand:

1. Pharmacies must certify in the Clozapine REMS Program to order and dispense clozapine
2. The risk of severe neutropenia associated with clozapine and the importance of ANC monitoring
3. There is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
4. Clozapine manufacturers, their agents and contractors may contact me to obtain names of our pharmacists to survey on the effectiveness of the program requirements for the Clozapine REMS Program

On behalf of the pharmacy, I agree to comply with the following program requirements:

5. My pharmacy will establish procedures and protocols that are subject to audit, to help ensure compliance with the requirements of the Clozapine REMS Program, including the following before dispensing clozapine:
 - All pharmacists and relevant staff involved in dispensing clozapine are trained and a record of the training is maintained
 - Verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program
 - Verify the ANC is current and acceptable or verify the prescriber's authorization for continuing clozapine treatment if the ANC is abnormal
 - Fill and dispense no more than the amount of clozapine necessary to treat the patient until the next blood draw/ANC or as directed by the prescriber
6. My pharmacy will establish procedures and protocols that are subject to audit, to not sell, loan, or transfer any clozapine inventory to any other pharmacy institution, distributor, or prescriber that is not enrolled in the Clozapine REMS Program
7. Pharmacies will renew enrollment in the Clozapine REMS Program every two years to maintain certification to order and dispense clozapine
8. Pharmacies will make available to the clozapine manufacturers and/or a designated third party or the FDA, documentation to verify understanding of, and adherence to, the requirements of the Clozapine REMS Program
9. Clozapine REMS Program personnel may contact my pharmacists to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
10. Provide dispensing location information to the Clozapine REMS Program
11. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

FOR INPATIENT PHARMACIES ONLY

12. Inpatient pharmacies are not required to obtain a Predispose Authorization (PDA) prior to dispensing clozapine.

Before dispensing clozapine to an inpatient for the first time, the inpatient pharmacies must:

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

Before dispensing clozapine to an inpatient for the first time, the inpatient pharmacies must:

1. Sign in into the Clozapine REMS Program website at www.clozapinerems.com, or
2. Call the Clozapine REMS Program contact center at 844-267-8678

Inpatient pharmacies must verify the ANC or prescriber's authorization for a patient to continue clozapine treatment in one of three ways:

1. By signing into the Clozapine REMS Program website at www.clozapinerems.com
2. By calling the Clozapine REMS Program contact center at 844-267-8678
3. By reviewing the patient's medical record in their hospital's medical record system

Prescribers or their designee(s) must submit ANC to the Clozapine REMS Program within 7 days of blood draw.

FOR OUTPATIENT PHARMACIES ONLY

12. Outpatient pharmacies must obtain a Predispose Authorization (PDA) before dispensing clozapine products to a patient to ensure compliance with the required safe use conditions.

Can your outpatient pharmacy management system adjudicate claims online?

Yes

By selecting "Yes", you are confirming that your pharmacy management system CAN support electronic communication with the Clozapine REMS Program using established telecommunications standards. Clozapine will be dispensed only after obtaining electronic authorization for all clozapine prescriptions, including cash claims, through your pharmacy management system. After submitting this form, you will receive instructions through the contact preference indicated in the authorized representative information section on how to submit test transactions to the Clozapine REMS Program. This is to ensure that your pharmacy management system has been successfully configured to allow for communication with the Clozapine REMS Program.

No

By selecting "No", you are confirming that your pharmacy management system CANNOT support electronic communication with the Clozapine REMS Program and you will access the Clozapine REMS Program website at www.clozapinerems.com or call the Clozapine REMS Program contact center to confirm safe use conditions (as outlined in attestation #5) before dispensing each clozapine prescription. A complete Predispose Authorization request requires the pharmacist to identify a unique patient, provide dispense information, and provide the prescriber's NPI or DEA.

Pharmacy Information (All Fields Required)

Pharmacy Name:

Pharmacy Type (select one): Inpatient Pharmacy Outpatient Pharmacy

Address:

City: _____ State: _____ Zip Code: _____

Inpatient Identifiers (At least one required)

NCPDP: _____ NPI: _____ DEA: _____

Outpatient Identifiers (NCPDP and NPI Required)

NCPDP: _____ NPI: _____ DEA: _____

Authorized Representative Information (All Fields Required)

First Name: _____ Last Name: _____

Credentials: R.Ph PharmD BCPS Other

Phone: _____ Fax: _____ Email: _____

Contact Preference (please select one): Email Fax

Authorized Representative Signature: _____

Date (MM/DD/YYYY): _____

Instructions for Prescribers

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

For enrollment via fax, please complete all required fields below and fax to 844-404-8876. For enrollment via the contact center, please call 844-267-8678. Enrollment confirmation will be sent via the contact preference specified on the prescriber's *Clozapine REMS Prescriber Enrollment Form*.

Complete this form for a patient if:

- This patient has never been treated with clozapine previously, OR
- If you have never treated this patient with clozapine (regardless of the patient's history of clozapine treatment)

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

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

If you have any questions, require additional information, or need further copies of Clozapine REMS Program documents, please visit the program website at www.clozapinerems.com, or call the Clozapine REMS Program at 844-267-8678.

PATIENT INFORMATION (All fields required for Enrollment)

First Name:	Last Name:
Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female	
Race: <input type="checkbox"/> Caucasian <input type="checkbox"/> African American <input type="checkbox"/> Asian <input type="checkbox"/> Hispanic <input type="checkbox"/> Other:	
Date of Birth (MM/DD/YYYY):	Zip Code:
Is this patient actively on clozapine therapy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	

LAB INFORMATION (ANC must be provided before clozapine is dispensed, but is not required for patient enrollment)

Blood Draw Date (MM/DD/YYYY):	ANC (per μ L):
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PRESCRIBER INFORMATION (All Fields Required)

Name:		
NPI or DEA:		
Phone:	Email:	Fax:
Submitter: <input type="checkbox"/> Prescriber <input type="checkbox"/> Prescriber Designee		

BENIGN ETHNIC NEUTROPENIA (BEN) PATIENT ATTESTATION* (Signature required only for attestation of BEN diagnosis)

By signing below, I attest that the above patient has Benign Ethnic Neutropenia (BEN).

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

*Enrollment for patients with BEN must be completed by faxing this signed document to 844-404-8876 or by accessing the Clozapine REMS Program website at www.clozapinerems.com.

Instructions for Prescribers

For immediate online Absolute Neutrophil Count (ANC) reporting please go to www.clozapinerems.com.

Use this form to submit ANC monitoring information or update patient information.

For INPATIENTS: The prescriber and in-patient pharmacist must review the ANC before clozapine can be dispensed. Submit ANC to the Clozapine REMS Program within 7 days of the blood draw date.

For OUTPATIENTS: The out-patient pharmacist must obtain a pre-dispense authorization (PDA) from the Clozapine REMS Program before clozapine can be dispensed.

- To obtain a PDA, a current and acceptable ANC must be reported to the Clozapine REMS Program or the prescriber must provide a treatment rationale (see Section 3) to authorize treatment if a patient's ANC indicates moderate to severe neutropenia (General Population) or severe neutropenia (Patients with BEN).

Section 1: ANC Lab Reporting

Prescriber Information (All Fields Required)

Name:		NPI or DEA:	
Phone:	Email:		Fax:
Submitter:	<input type="checkbox"/> Prescriber	<input type="checkbox"/> Prescriber Designee	<input type="checkbox"/> Pharmacy

Patient Information (All Fields Required)

Name		
Date of Birth (MM/DD/YYYY):	Zip Code:	Gender:

ANC Monitoring (All Fields Required)

Blood Draw Date (MM/DD/YYYY):	ANC (per μ L):
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Section 2: Patient Updates (if applicable)

Change Treatment Status

Complete this section if you want to change this patient's treatment status. If this section is left blank, no changes will be made.

I want to change this patient's treatment status to: **(check one)**

- Active (restarting or continuing clozapine requires a treatment rationale for patients with moderate or severe neutropenia. Please refer to the "Treatment Rationale" section)
- Interrupted
- Discontinued

Change Monitoring Frequency

Complete this section if you want to change this patient's monitoring frequency. If this section is left blank, no changes will be made.

Based on the clozapine prescribing information, my patient is eligible for a change in ANC monitoring frequency. I want to change the ANC monitoring frequency to: **(check one)**

- Weekly
- Every 2 weeks
- Every 4 weeks

Section 3: Prescriber Authorization

Treatment Rationale*

Complete this section if the patient has moderate neutropenia (ANC 500-999/ μ L for the General Population) or severe neutropenia (ANC < 500/ μ L for General Population and Patients with BEN) and you want to continue treatment.

The treatment rationale is **(check one and sign below):**

- Benefits of continuing clozapine treatment outweigh risk of neutropenia
 - Until next ANC Lab
 - Until (MM/DD/YYYY) _____
No more than 6 months from today
- Patient has Benign Ethnic Neutropenia (BEN) (No Expiration)

Hospice Care*

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver.

If you want to change the monitoring frequency to once every 6 months for a hospice patient, **check the box and sign below:**

- This is a hospice patient.

Authorizing Prescriber Information (All Fields Required)

Name:		NPI or DEA:	
Authorizing Prescriber Signature:		Date (MM/DD/YYYY):	

**Authorizing Prescriber Signature is required for a change in treatment rationale, and/or for a hospice care patient.*

CLOZAPINE REMS

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

Clozapine and the Risk of Neutropenia:

A Guide for Healthcare Providers

This Guide discusses:

- What is the Clozapine REMS Program?
- Clozapine and the risk of severe neutropenia
- Treatment recommendations and patient ANC monitoring
- Prescriber requirements for the Clozapine REMS Program
- Pharmacy requirements for the Clozapine REMS Program

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1 The Clozapine REMS Program

Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/ μ L). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single, shared program called the **C**lozapine **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Program. A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs, and is required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia.

The Clozapine REMS Program provides a **centralized** point of access:

1. For **prescribers** and **pharmacies** to certify before prescribing or dispensing clozapine
2. To enroll and manage **patients** on clozapine treatment

Clozapine is available by prescription as:

- Clozaril® (clozapine) tablets, for oral use
- Fazaclo® (clozapine, USP) orally disintegrating tablets
- Versacloz® (clozapine, USP) oral suspension
- Approved generic equivalents of these products

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

Prescribers

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

Pharmacies

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

Patients

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

2 ANC, Neutropenia, and Patient ANC Monitoring

What is ANC?

ANC is the laboratory parameter for monitoring patients for clozapine-induced neutropenia. Prescribers must report the ANC before starting and during clozapine treatment.

ANC is usually available as a component of the complete blood count (CBC), including differential:

- ANC is more relevant to drug-induced neutropenia than white blood cell (WBC) count
- ANC may also be calculated using the following formula:

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

* neutrophil includes "segs" and "bands"

Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary.

What is the risk of severe neutropenia associated with clozapine?

Clozapine can cause severe neutropenia, which can lead to serious infections and death. Severe neutropenia occurs in a small percentage of patients taking clozapine.

- Severe neutropenia is defined as ANC less than 500/ 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 ANC's are lower than "standard" laboratory ranges for neutrophils. Because of this condition, patients who have been diagnosed with BEN have a separate ANC monitoring algorithm when treated with clozapine.



When enrolling a patient in the Clozapine REMS Program, identify if the patient has been diagnosed with BEN, so the patient is monitored according to the correct ANC monitoring algorithm.

A few important things to know about patients diagnosed with BEN:

- It is most commonly observed in individuals of African descent (approximate prevalence of 25-50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin
- BEN is more common in men
- Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections
- Patients with BEN **are not** at increased risk for developing clozapine-induced neutropenia

Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider a hematology consultation before starting or during clozapine treatment as necessary.

What are the treatment recommendations and monitoring requirements for patients taking clozapine?

The recommended ANC monitoring schedules for patients in the General Population as well as patients who have been diagnosed with BEN are shown in **Table 1**. The table also provides recommendations for monitoring patients who experience a decrease in ANC during the course of treatment.

Patients may transition to less frequent ANC monitoring based on the number of weeks of continuous clozapine therapy and the patient's ANCs. Weekly ANC monitoring is required for all patients during the first six months of treatment. If the ANC remains in the normal range (ANC greater than or equal to 1500/ μ L for the General Population, ANC greater than or equal to 1000/ μ L for Patients with BEN) for the first six months of therapy, monitoring frequency can be reduced to every 2 weeks.

If the patient's ANC continues to remain in the normal range for the second six months of treatment, ANC monitoring may be reduced to once every 4 weeks.

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



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

- at least 1500/ μ L for the General Population
- at least 1000/ μ L for patients diagnosed with BEN

During treatment, monitor ANC regularly as described in **Table 1** below.

Tabl 1: R comm n Moni oring Fr qu ncy an Clinical D cisions by ANC L v l

ANC L v l	Tr a men R comm n a ion	ANC Moni oring
<p>Normal Rang for a N w Pa i n a GENERAL POPULATION</p> <ul style="list-style-type: none"> ANC a 1500/μL 	<ul style="list-style-type: none"> Initi te tre tment If tre tment interrupted: <ul style="list-style-type: none"> < 30 d ys, continue monitoring as before ≥ 30 d ys, monitor as if new p tient a Discontin uation for re asons other th a neutropeni 	<ul style="list-style-type: none"> Weekly from initi tion to six months Every 2 weeks from 6 to 12 months a Monthly after 12 months a See Section 2.4 of the full Prescribing Inform tion
<p>Mil d a u rop nia (1000 - 1499/μL)* a</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Continue tre tment a 	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Three times weekly until ANC a 1500/μL Once ANC a 1500/μL return to patient's l st "Normal Range" ANC monitoring interv l**
<p>Mo ra a N a u rop nia (500 - 999/μL)* a</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Recommend hem tology consult tion Interrupt treatment for suspected cloz pine induced neutropeni Resume tre tment once ANC norm lizes to a 1000/μL 	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> D aily until ANC a 1000/μL, then Three times weekly until ANC a 1500/μL Once ANC a 1500/μL check ANC weekly for 4 weeks, then return to patient's l st "Normal Range" ANC monitoring interv l**
<p>S v a d N a u rop nia (< 500/μL)* a</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> Recommend hem tology consult tion Interrupt treatment for suspected cloz pine induced neutropeni Do not rech denge unless prescriber determines benefits outweigh risks a 	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> D aily until ANC a 1000/μL Three times weekly until ANC a 1500/μL If p tient rech danged, resume tre tment a new p tient under "Normal Range" monitoring once ANC \geq 1500/μL a

* Confirm ll initi l reports of ANC less th a 1500/ μ L (ANC \leq 1000/ μ L for BEN p aients) with a repe d ANC me surement within 24 hours a

** If clinic lly p propri te

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

For Patients in the General Population

Yes. Prescribers may choose to continue clozapine treatment in patients with ANCs less than 1000/ μ L. However, prescribers should follow the treatment recommendations as noted in **Table 1** and carefully determine if the benefits of continuing clozapine treatment outweigh the risks.

The recommendations to interrupt treatment are provided to ensure patient safety. If monitoring ANC and symptoms of infection is not done appropriately, patients with ANCs less than 1000/ μ L are at risk of developing complications of severe neutropenia (including death).

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

For Patients with BEN

Yes. The Prescribing Information for clozapine recommends interrupting clozapine treatment for patients with BEN only when the ANC is *less than 500/ μ L*. No interruption in treatment is recommended for ANC 500-999/ μ L, although a hematology consultation is recommended.

If a patient develops a fever, how is clozapine treatment managed?

Generally, clozapine treatment should be interrupted as a precautionary measure in any patient who develops a fever of 38.5°C (101.3°F) or greater, and an ANC should be obtained. Fever is often the first sign of a neutropenic infection.

If fever occurs in any patient with an ANC less than 1000/ μ L, initiate appropriate neutropenia workup and treatment for infection. Refer to **Table 1** for ANC monitoring recommendations.

If any patient presents with evidence of fever and/or neutropenia, consider a hematology consultation. **r**

How is clozapine discontinued for neutropenia?

The method of treatment discontinuation will vary depending on the patient’s last ANC. Abrupt treatment discontinuation is necessary for moderate to severe neutropenia that you suspect is caused by clozapine.



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



By signing into the Clozapine REMS Program website at www.clozapinerems.com



By calling the Clozapine REMS Program contact center at 844-267-8678



By completing the “Patient Update – Change Treatment Status” section of the *ANC Lab Reporting Form* and faxing it to the Clozapine REMS Program at 844-404-8876

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

After **discontinuing** clozapine, monitor ANC according to the recommendations in **Table 1** as shown below.

<p>Moderate Neutropenia (500 to 999/μL)*</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> • Daily until ANC \geq 1000/μL, then • Three times weekly until ANC \geq 1500/μL
<p>Severe Neutropenia (less than 500/μL)*</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> • Daily until ANC \geq 1000/μL, then • Three times weekly until ANC \geq 1500/μL <p>BEN POPULATION</p> <ul style="list-style-type: none"> • Daily until ANC \geq 500/μL • Three times weekly until ANC \geq patients established baseline

* Confirm all initial reports of ANC less than 1500/ μ L (ANC < 1000/ μ L for BEN patients) with a repeat ANC measurement within 24 hours

- Monitor ANC in any patient reporting a fever (temperature of 38.5°C or 101.3°F or greater) during the 2 weeks after discontinuation
- Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea
- For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for General Population patients until their ANC is greater than or equal to 1500/ μ L and for Patients with BEN until their ANC is greater than or equal to 1000/ μ L or above their baseline

Refer to Section 2.4 of the clozapine Prescribing Information for further information

Can a patient be rechallenged with clozapine?

Yes. For some patients who experience, or have experienced, moderate clozapine-related neutropenia (ANC less than 1000/ μ L) or severe clozapine-related neutropenia (ANC less than 500/ μ L), the risk of serious psychiatric illness from discontinuing clozapine may be greater than the risk of rechallenge. This may be relevant for patients with severe schizophrenic illness who have no treatment option other than clozapine.

In making the decision to rechallenge a patient, consider:

- a hematology consult
- the ANC ranges defined in the full Prescribing Information
- the patient's medical and psychiatric history
- a discussion with the patient and his or her caregiver about the benefits and risks of clozapine rechallenge
- the severity and characteristics of the neutropenic episode







Refer to Section 2.5 Re-initiation of Treatment in the clozapine Prescribing Information for more information on how to restart clozapine in patients who have discontinued clozapine. **r**

3 Clozapine REMS Program Requirements for Prescribers

What is the role of prescribers in the Clozapine REMS Program?

Step 1: Review the full Prescribing Information for clozapine

Step 2: Certify in the Clozapine REMS Program by:

-   Reviewing *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
-   Passing the *Knowledge Assessment for Healthcare Providers*
-   Completing the *Clozapine REMS Prescriber Enrollment Form*

Step 3: Enroll every new patient in the Clozapine REMS Program

Step 4: Counsel each patient (or their caregiver) about the risk of severe neutropenia

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

Step 6: Report each ANC for each patient to the Clozapine REMS Program

Step 7: Provide authorization to continue treatment, if necessary, through the Clozapine REMS Program when the patient's ANC results meet criteria for interruption of therapy and you decide to continue clozapine treatment.

Refer to the section titled "What is a treatment rationale?" on page 13 for more details on how to authorize a patient to continue treatment.



Prescribers may designate other healthcare providers or office staff to enroll patients and enter ANC results on the prescriber's behalf.



Find more information about designees at www.clozapinerems.com.



What do I tell my patients about clozapine?

Use the patient counseling tool titled *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*. Review this information with patients or their caregivers as often as needed to ensure they understand the risk of neutropenia associated with clozapine and the importance of ANC monitoring. Refer to Section 17 of the clozapine Prescribing Information for additional important counseling messages for your clozapine patients.

You may choose not to provide *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers* to the patient or caregiver, if you determine that the patient's adherence to clozapine treatment will be negatively impacted by providing it.

How do I enroll a patient?

You can enroll a patient one of two ways:

-  By signing into the Clozapine REMS Program website at www.clozapinerems.com and enrolling the patient online
-  By downloading a *Clozapine REMS Patient Enrollment Form* from the Clozapine REMS Program website at www.clozapinerems.com, and faxing the completed form to 844-404-8876.

Complete a *Clozapine REMS Patient Enrollment Form* if:

- The patient has never been treated with clozapine before, or
- If you have never treated this patient with clozapine, regardless of the patient's history of clozapine treatment

What if my patient has been treated with clozapine before?

If you have treated the patient with clozapine after **October 1, 2012** and that patient was registered in any of the individual clozapine patient registries, the patient's information is listed in the Clozapine REMS Program where you can access the patient's profile.

Patient information before **October 1, 2012** was not transferred into the Clozapine REMS Program, unless the patient was listed in the National Non-Rechallenge Master File (NNRMF) (see the following Section for a definition of the NNRMF).

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

If you cannot find the patient, contact the REMS program at 844-267-8678 for assistance or re-enroll the patient.

If you would like to inquire about a patient's previous clozapine history before enrolling the patient, please call the Clozapine REMS Program at 844-267-8678 for assistance.

How do I find out if my patient was listed in the National Non-Rechallenge Master File (NNRMF)?

Patients were listed in the NNRMF if a patient had a WBC less than 2,000/μL or an ANC less than 1,000/μL.



All patients who were listed in the NNRMF and all their lab data were transferred into the Clozapine REMS Program. These patients are identified with a red flag in the Clozapine REMS Program at www.clozapinerems.com.

To access patient information through the Clozapine REMS Program, you must enroll the patient. If you would like to inquire about a patient's previous clozapine history before enrolling the patient, please call the Clozapine REMS Program at 844-267-8678 for assistance.

How do I report ANC results for my patients?

For Outpatients:

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

For Inpatients: If your patient is hospitalized...

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

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



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

For both Inpatients and Outpatients:

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



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



By calling the Clozapine REMS Program contact center at 844-267-8678



By faxing the ANC results to the Clozapine REMS Program at 844-404-8876

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



What is a treatment rationale?

When a patient's ANC is less than 1000/ μ L (General Population) or less than 500/ μ L (Patients with BEN), a prescriber may authorize clozapine treatment to continue. This authorization, called a treatment rationale, requires the prescriber to confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia.

How do I report a treatment rationale?

- The Clozapine REMS Program will alert the prescriber if an ANC is provided that is below the recommended thresholds for a patient. Clozapine will not be dispensed to the patient unless the prescriber provides a treatment rationale to authorize continued treatment
- The Clozapine REMS Program will change the treatment status of a patient with a low ANC to "interrupted" or "discontinued", according to the recommendations in the Prescribing Information, found in **Table 1** above
- If the prescriber wishes to continue clozapine treatment, the prescriber must change the patient's treatment status to "active", and confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (i.e., the 'treatment rationale')

Prescribers must confirm treatment continuation one of two ways:

-  By signing into the Clozapine REMS Program website at www.clozapinerems.com
-  By faxing a signed *ANC Lab Reporting Form* to 844-404-8876 with a completed "Treatment Rationale" section

- After the prescriber provides the treatment rationale, the Clozapine REMS Program will issue a Predispose Authorization (PDA) which allows the outpatient pharmacy to dispense clozapine
- Information provided in the Clozapine REMS Program is not a substitute for appropriate documentation in the patient's medical record regarding the prescriber's decision to continue, interrupt, or discontinue clozapine treatment

What if my clozapine patient is under hospice care?

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every six months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychiatric symptoms and the patient's terminal illness.

4 Clozapine REMS Program Requirements for Pharmacies

What types of pharmacies must be certified?

All inpatient and outpatient pharmacies must certify in the Clozapine REMS Program to purchase and dispense clozapine. The requirements for outpatient pharmacies are different from the requirements for inpatient pharmacies. The different requirements are explained in Section “What are the requirements for different pharmacy types?”

The designated authorized representative for the pharmacy will complete the *Pharmacy Enrollment Form*. This form is to certify a single inpatient *or* a single outpatient pharmacy location.

- **For outpatient pharmacies**, the authorized representative must confirm if your pharmacy management system can or cannot support electronic communication with the Clozapine REMS Program to verify the Clozapine REMS Program safe use requirements.
- **For inpatient pharmacies**, a pharmacy management system that supports electronic communication with the Clozapine REMS Program is not needed.

The authorized representative for the pharmacy or pharmacies can certify the pharmacy online or by fax. Certifying multiple pharmacy locations must be done online.

What is an authorized representative?

In general, an authorized representative for a pharmacy:

- coordinates the activities required in the Clozapine REMS Program
- establishes and implements processes and procedures to ensure compliance with the safe use conditions required in the Clozapine REMS Program

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

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

- Pharmacy Manager
- Staff Pharmacist

If your pharmacy has more than one pharmacy location and your organization would like to coordinate staff training and implement processes for all the pharmacies in your organization, the authorized representative may be a:

- Director of Pharmacy Services
- Corporate Executive overseeing Pharmacy Service

What is a Predispense Authorization (PDA)?




Before dispensing clozapine to an **outpatient**, the pharmacy must obtain a Predispense Authorization, or PDA, from the Clozapine REMS Program. A PDA is an electronic code that indicates the Clozapine REMS Program has verified:

- Patient is enrolled in the Clozapine REMS Program
- Prescriber is certified in the Clozapine REMS Program
- Pharmacy is certified in the Clozapine REMS Program
- ANC is current (reported within 7 days of the blood draw)
- ANC is within an acceptable range, or the prescriber provided a treatment rationale



Once a PDA is obtained, the outpatient pharmacy can dispense clozapine to the patient.

Obtain a PDA in one of three ways:

-  By enabling your pharmacy management system to support electronic communication with the Clozapine REMS Program
-  By signing into Clozapine REMS Program website at www.clozapinerems.com
-  By calling the Clozapine REMS Program contact center at 844-267-8678







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

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

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

Step 1: Review the full Prescribing Information for dozapine

Step 2: Certify in the Clozapine REMS Program by:

-   Reviewing *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
-   Passing the *Knowledge Assessment for Healthcare Providers*
-   Completing the *Clozapine REMS Pharmacy Enrollment Form*

Step 3: Ensure training for all relevant staff involved in the dispensing of clozapine on the Clozapine REMS Program requirements

Step 4: Put processes and procedures in place to verify:

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

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

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

How you verify the patient is authorized to receive clozapine depends on your pharmacy type and your pharmacy's telecommunication capabilities.

Outpatient Pharmacies WITH Electronic Telecommunication Verification

Certification

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

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

Dispensing

Before you dispense clozapine to each patient, you must:

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

Once a PDA is obtained, you can dispense clozapine to the patient

- You do not need to document the PDA on the prescription or in your pharmacy management system



Dispensing Information for **All Pharmacies**

- The amount of clozapine that can be dispensed depends on when the patient's next blood draw is, according to the monitoring requirements
- Pharmacies should dispense enough medication to treat the patient with clozapine until the next blood draw/ANC or as directed by the prescriber
- If you do not receive a PDA, you will receive a message explaining why you are not authorized to dispense clozapine to the patient



Outpatient Pharmacies WITHOUT Electronic Telecommunication Verification

Certification

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

Dispensing

Obtain a PDA in one of two ways:

-  By signing into Clozapine REMS Program website at www.clozapinerems.com
-  By calling the Clozapine REMS Program contact center at 844-267-8678

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

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

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

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

Once a PDA is obtained, you can dispense clozapine to the patient. You do not need to document the PDA on the prescription or in your pharmacy management system. If you do not receive a PDA, the Clozapine REMS Program will explain why you are not authorized to dispense clozapine to the patient.

Inpatient Pharmacies

Certification

As part of certification in the Clozapine REMS Program, the authorized representative for your pharmacy must implement processes to comply with program requirements.

Dispensing

Obtaining a PDA is not required in an inpatient setting.

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

Step 1: Access the Clozapine REMS Program by:

-  Signing into the website at www.clozapinerems.com, or
-  Calling the Clozapine REMS Program contact center at 844-267-8678




Step 2: Provide the following information:

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

Step 3: Verify patient eligibility to receive clozapine by:

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

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

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

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

5 Reporting Adverse Events Associated with Clozapine

Report suspected adverse events directly to the Clozapine REMS Program at 844-267-8678. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500A, available at www.fda.gov/medwatch.

6 Clozapine REMS Program Information and Resources

Additional Clozapine REMS Program information and resources are available online at www.clozapinerems.com or by contacting the Clozapine REMS Program contact center at 844-267-8678.

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

Question 1

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

- A. True
- B. False

Question 2

Clozapine is associated with severe neutropenia.

- A. True
- B. False

Question 3

Severe neutropenia is defined as:

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

Question 4

Before initiating treatment with clozapine:

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

Question 5

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

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

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

Name: _____ NPI: _____ Fax: _____

Question 6

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

- A. True
- B. False

Question 7

Before clozapine can be dispensed, a pharmacist must:

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

Question 8

How much clozapine can be dispensed?

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

Question 9

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

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

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

Name: _____ NPI: _____ Fax: _____

Question 10

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

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

Question 11

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

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

Question 12

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

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

Question 13

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

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

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

Name: _____ NPI: _____ Fax: _____

CLOZAPINE REMS

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

A Guide for Patients and Caregivers:

What You Need to Know about Clozapine
and Neutropenia

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 information about clozapine treatment?

Clozapine can cause severe neutropenia. Neutropenia is a blood disorder that occurs when a certain type of white blood cells called neutrophils are not made or not enough of them are made. This makes it harder for your body to fight infections.

Before you can start clozapine **and** during treatment, you must have regular blood tests to measure the number of neutrophils you have in your blood. 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.

This is not the only serious risk associated with clozapine treatment. Talk to your doctor about the other serious risks.

What are the symptoms of neutropenia?

You might not have any symptoms at all. Getting your blood tested to measure the number of neutrophils is the only way to check for neutropenia. This helps your doctor know if you are more likely to get an infection.



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

- 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

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 or feel sick

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

Because of the risk of developing severe neutropenia, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for clozapine. The purpose of the Clozapine REMS Program is to make sure that the benefits of clozapine treatment outweigh the risks.

What are the Clozapine REMS Program requirements for me?

To receive clozapine:

1. **Review this Guide** with your doctor, pharmacist, or nurse
2. Ask questions! **Make sure you understand** what you need to do to take part in the Clozapine REMS Program
3. **Get your blood tested** as directed by your doctor
You must get your blood tested before you can receive clozapine from your pharmacy
4. **Pick up your clozapine prescription** from a pharmacy that is part of the Clozapine REMS Program. Your doctor will help you find a pharmacy that participates in the Clozapine REMS Program
5. **Tell your doctor right away** if you suffer any flu-like illness or fever while taking clozapine

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
 - Every 4 weeks after the first year if your ANC stays normal

Monitoring Results

- If your ANC is too low, your doctor will schedule blood tests more frequently

Stay on Clozapine

- The Clozapine REMS Program will keep track of your blood test results so your doctor and pharmacist know if it is safe to fill your clozapine prescription

No Blood, No Drug

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

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 Program at [844-267-8678](tel:844-267-8678).

You can also report negative side effects to the FDA at www.fda.gov/medwatch, or call [800-FDA-1088](tel:800-FDA-1088).

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Clozapine MS Program Website Scraps 2

September 2015

CLOZAPINE REMS

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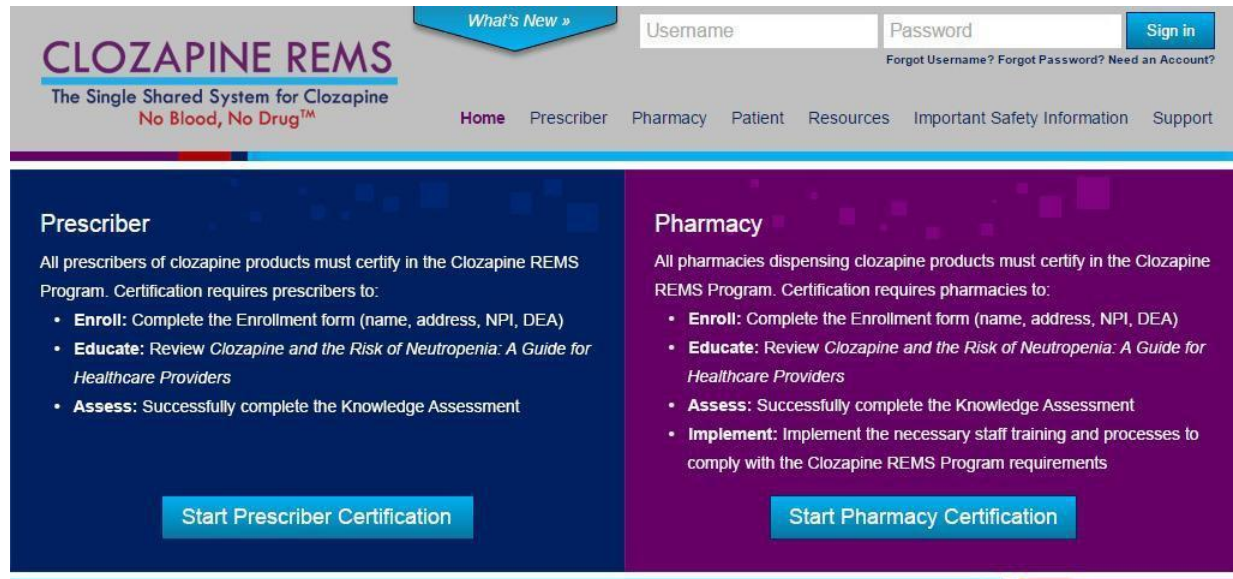
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. Static Pages 1

. Home Page



The screenshot shows the home page of the Clozapine REMS program. At the top left is the logo "CLOZAPINE REMS" with the tagline "The Single Shared System for Clozapine No Blood, No Drug™". To the right is a navigation menu with links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. A "What's New" button is also present. Below the navigation is a login section with fields for Username and Password, and a "Sign in" button. Below the login section are two main content areas: "Prescriber" and "Pharmacy". Each area contains a brief description of the certification requirements and a list of steps: Enroll, Educate, and Assess. The "Pharmacy" section also includes an "Implement" step. At the bottom of each section is a button to "Start [Prescriber/Pharmacy] Certification".

What is the Clozapine REMS Program?

Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/ μ L). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single, shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS). A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs, and is required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia. The Clozapine REMS Program replaces the individual clozapine patient registries and the National Non-Rechallenge Master File (NNRMF).

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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1 2 Site Guide – Prescriber Tab .



Site Guide

This website provides users the ability to become certified in the Clozapine REMS Program, enroll patients on clozapine, and track patient ANC values.

The links located at the top and bottom of every page offer information for prescribers, pharmacists, and patients. Additional information about the program is also available under **Resources** and through the **FAQs**, **Site Map**, and **Contact Us** links.

Prescriber Pharmacy Patient Designee Pharmacy Staff

Prescribers will begin the certification process by using the **Learn More** button below, which will navigate the prescriber to the certification landing page or by visiting the **Prescriber** link at the top of the page.

The **Prescriber** page provides specific steps that must be completed to prescribe clozapine. From the **Prescriber** page, prescribers can use the **Begin Now** button to start their certification process.

Once signed into the site and your certification is complete, you can navigate to your **My Dashboard** page to perform various activities that support the Clozapine REMS Program requirements such as enrolling patients and adding ANC values. The **My Dashboard** page is the main portal for all activities performed on this site.

During specific activities, a *progress bar* will guide you through the required activity from start to finish.

[Learn More](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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1 3 Site Guide – Pharmacy Tab .



Site Guide

This website provides users the ability to become certified in the Clozapine REMS Program, enroll patients on clozapine, and track patient ANC values.

The links located at the top and bottom of every page offer information for prescribers, pharmacists, and patients. Additional information about the program is also available under **Resources** and through the **FAQs**, **Site Map**, and **Contact Us** links.

Prescriber **Pharmacy** Patient Designee Pharmacy Staff

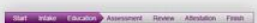


Authorized representatives for a pharmacy will begin the certification process by using the **Learn More** button below, which will navigate the authorized representative to the certification landing page or by visiting the **Pharmacy** link at the top of the page.

The **Pharmacy** page provides specific steps that must be completed to dispense clozapine. From the **Pharmacy** page, authorized representatives can use the **Begin Now** button to start their certification process.

Once signed into the site and your certification is complete, you can navigate to your **My Dashboard** page to perform various activities that support the Clozapine REMS Program requirements such as adding ANC values and requesting predispense authorizations. The **My Dashboard** page is the main portal for all activities performed on this site.

During specific activities, a *progress bar* will guide you through the required activity from start to finish.

[Learn More](#)



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1 4 Site Guide – Patient Tab .



Site Guide

This website provides users the ability to become certified in the Clozapine REMS Program, enroll patients on clozapine, and track patient ANC values.

The links located at the top and bottom of every page offer information for prescribers, pharmacists, and patients. Additional information about the program is also available under **Resources** and through the **FAQs**, **Site Map**, and **Contact Us** links.

Prescriber Pharmacy **Patient** Designee Pharmacy Staff

This site is for prescribers and pharmacists with patients on clozapine therapy. Patients must be enrolled in the program by a certified prescriber. If you believe you should be enrolled in the Clozapine REMS Program, please talk to your prescriber.

Additional information is available to patients by using the **Learn More** button below, which will navigate the patient to the patient information page or by visiting the **Patient** link at the top of the page.

[Learn More](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.5 Site Guide – Designee Tab 1



Site Guide

This website provides users the ability to become certified in the Clozapine REMS Program, enroll patients on clozapine, and track patient ANC values.

The links located at the top and bottom of every page offer information for prescribers, pharmacists, and patients. Additional information about the program is also available under **Resources** and through the **FAQs**, **Site Map**, and **Contact Us** links.

Prescriber Pharmacy Patient **Designee** Pharmacy Staff

Prescriber Designees can learn more about the certification process by using the **Learn More** button below, which will navigate the prescriber designee to the certification landing page or by visiting the **Prescriber** link at the top of the page.

The **Prescriber Designee Certification** page provides specific steps that must be completed to manage patients. From the **Prescriber Designee** page, prescriber designees can use the **Begin Now** button to start their certification process.

Once signed into the site and your certification is complete, you can navigate to your **My Dashboard** page to perform various activities that support the Clozapine REMS Program requirements such as enrolling patients and adding ANC values. The **My Dashboard** page is the main portal for all activities performed on this site.

During specific activities, a *progress bar* will guide you through the required activity from start to finish.

[Learn More](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.6 Site Guide – Pharmacy Staff Tab 1



Site Guide

This website provides users the ability to become enrolled in the Clozapine REMS Program, enroll patients on clozapine, and track patient ANC values.

The links located at the top and bottom of every page offer information for prescribers, pharmacists, and patients. Additional information about the program is also available under **Resources** and through the **FAQs**, **Site Map**, and **Contact Us** links.

Prescriber Pharmacy Patient Designee **Pharmacy Staff**



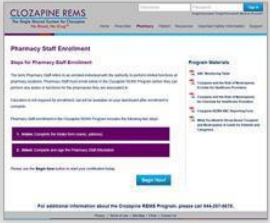
Pharmacy Staff can learn more about the enrollment process by using the **Learn More** button below which will navigate the pharmacy staff to the enrollment landing page or by visiting the **Pharmacy** link at the top of the page.

The **Pharmacy Staff** page provides specific steps that must be completed to dispense clozapine. From the **Pharmacy Staff Enrollment** page, pharmacy staff members can use the **Begin Now** button to start their enrollment process.

Once signed into the site and your enrollment is complete, you can navigate to your **My Dashboard** page to perform various activities that support the Clozapine REMS Program requirements such as adding ANC values and requesting predispense authorizations. The **My Dashboard** page is the main portal for all activities performed on this site.

During specific activities, a *progress bar* will guide you through the required activity from start to finish.

[Learn More](#)



For additional information about the Clozapine REMS Program, please call 844-267-8678.

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1 7 Prescriber Certification .



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[Home](#) **Prescriber** [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Prescriber Certification

Steps for Prescriber Certification

Prescribers must be certified in the Clozapine REMS Program to prescribe clozapine.

If you choose to allow designees to act on your behalf, each designee must be certified in the Clozapine REMS Program. For more information on the designee certification process, please go to [Prescriber Designee Certification](#).

Certification in the Clozapine REMS Program includes the following three steps:

1. Enroll: Complete the Enrollment form (name, address, NPI, DEA)

2. Educate: Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*

3. Assess: Successfully complete the Knowledge Assessment

If your browser closes during certification, you can come back to the same point in the process.

Please use the **Begin Now** button to start your certification today.

[Begin Now!](#)

Program Materials

-  [ANC Monitoring Table](#)
-  [Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers](#)
-  [Clozapine REMS ANC Lab Reporting Form](#)
-  [Clozapine REMS Prescriber Enrollment Form](#)
-  [What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.8 Prescriber Designee Certification 1

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Home **Prescriber** Pharmacy Patient Resources Important Safety Information Support

Username Password [Sign in](#)
Forgot Username? Forgot Password? Need an Account?

Prescriber Designee Certification

Steps for Prescriber Designee Certification

The term designee refers to any person who has been designated or requested to perform some duty or function on behalf of a certified prescriber. Designees must be certified and approved in the Clozapine REMS Program before they can perform any duties or functions for their prescriber.

If you want to associate yourself to a pharmacy and have selected the Prescriber Designee Certification by accident, please go to [Pharmacy Staff Enrollment](#).

Prescriber designee certification in the Clozapine REMS Program includes the following three steps:

1. Enroll: Complete the Enrollment form (name, address)

2. Educate: Review the REMS requirements

3. Confirm: Understanding of the requirements of the REMS

If your browser closes during certification, you can come back to the same point in the process.

Please use the **Begin Now** button to start your certification today.

[Begin Now!](#)

Program Materials

-  [ANC Monitoring Table](#)
-  [Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers](#)
-  [Clozapine REMS ANC Lab Reporting Form](#)
-  [Clozapine REMS Prescriber Designee Education Program](#)
-  [Clozapine REMS Prescriber Designee Enrollment Form](#)
-  [What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

.9 Pharmacy Certification 1

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Pharmacy Certification

Steps for Pharmacy Certification

All inpatient and outpatient pharmacies must be certified in the Clozapine REMS Program in order to purchase and dispense clozapine. Certification requires the identification of an authorized representative for the pharmacy to complete the certification process. The authorized representative must ensure all pharmacists with privileges to dispense understand that clozapine is only available to certified pharmacies through the Clozapine REMS Program.

Pharmacy Staff must enroll in the Clozapine REMS Program to obtain a PDA from the REMS website, to enter ANC, verify the prescriber is certified, or verify the patient is enrolled. If the pharmacy is a non-switch pharmacy, to comply with the REMS the pharmacy staff will either need to obtain a PDA by calling the program or by signing into the website. For more information on the Pharmacy Staff enrollment process, please go to [Pharmacy Staff Enrollment](#).

Certification in the Clozapine REMS Program includes the following three steps:

- 1. Enroll:** Complete the Enrollment form (name, address, NPI, DEA)
- 2. Educate:** Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
- 3. Assess:** Successfully complete the Knowledge Assessment
- 4. Implement:** Implement the necessary staff training and processes to comply with the Clozapine REMS Program requirements

If your browser closes during certification, you can come back to the same point in the process.

Please use the **Begin Now** button to start your certification today.

[Begin Now!](#)

Program Materials

-  [ANC Monitoring Table](#)
-  [Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers](#)
-  [Clozapine REMS ANC Lab Reporting Form](#)
-  [Clozapine REMS Chain Pharmacy Enrollment Form](#)
-  [Clozapine REMS Pharmacy Enrollment Form](#)
-  [What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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1 10 Pharmacy Staff Enrollment .

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Pharmacy Staff Enrollment

Steps for Pharmacy Staff Enrollment

Pharmacy Staff may include pharmacists or other individuals who assist in dispensing medication in a pharmacy. If your pharmacy is certified to dispense clozapine, Pharmacy Staff can enroll in the Clozapine REMS Program to have access to the Clozapine REMS Program website. Pharmacy Staff can link to multiple REMS certified pharmacy locations.

Pharmacy Staff enroll by creating an online account. Education is not required for enrollment but will be available after your enrollment is complete through your Authorized Representative.

For Outpatient Pharmacies: Pharmacy Staff must enroll in the Clozapine REMS Program to obtain a pre-dispense authorization (PDA) before dispensing each clozapine prescription. Pharmacy Staff who are enrolled can obtain a PDA by calling the Clozapine REMS Contact Center or through electronic claim adjudication if your pharmacy has set up that process. Talk to your authorized representative if you are not sure how your pharmacy must obtain a PDA.

Pharmacy Staff must enroll to obtain a PDA through the Clozapine REMS website.

For Inpatient Pharmacies: Pharmacy Staff must enroll to perform eligibility checks through the Clozapine REMS website or the Clozapine REMS Contact Center.

Pharmacy staff enrollment in the Clozapine REMS Program includes the following two steps.





1. **Enroll:** Complete the enrollment form (name, address)

2. **Attest:** Complete and sign the Pharmacy Staff Attestation

Please use the **Begin Now** button to start your enrollment today.

[Begin Now!](#)

Program Materials

-  [ANC Monitoring Table](#)
-  [Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers](#)
-  [Clozapine REMS ANC Lab Reporting Form](#)
-  [What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Patient Information

Because of the risk of developing severe neutropenia, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for clozapine.

The purpose of the Clozapine REMS Program is to make sure that the benefits of clozapine treatment outweigh the risks.

Prescribers must talk to their patients about the Clozapine REMS Program requirements and the risks of using clozapine. Patients should review the *What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers* program material and talk with their prescriber if they have questions or concerns about using clozapine.

Program Materials

 **What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers**

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Program Materials

Forms	Patient	Pharmacy	Prescriber	Wholesaler/Distributor
 Clozapine REMS ANC Lab Reporting Form				
 Clozapine REMS Chain Headquarters Pharmacy Enrollment Form				
 Clozapine REMS Patient Enrollment Form				
 Clozapine REMS Pharmacy Enrollment Form				
 Clozapine REMS Prescriber Designee Enrollment Form				
 Clozapine REMS Prescriber Enrollment Form				

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Resources included under the other tabs are listed below:

- Patient
 - What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers
 - Clozapine REMS Patient Enrollment Form
 - Clozapine REMS ANC Lab Reporting Form
- Pharmacy
 - What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers
 - Dear Healthcare Provider Letter
 - Clozapine REMS Pharmacy Enrollment Form
 - Clozapine REMS Chain Headquarters Pharmacy Enrollment Form
 - Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers
 - Clozapine REMS Patient Enrollment Form
 - Clozapine REMS ANC Lab Reporting Form
 - Important Safety Information

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- NC Calculator
 - NC Monitoring Table
- Prescriber
 - What You Need to Know about Clozapine and Neutropenia: Guide for Patients and Caregivers
 - Dear Healthcare Provider Letter
 - Clozapine REMS Prescriber Enrollment Form
 - Clozapine REMS Prescriber Designee Enrollment Form
 - Clozapine and the Risk of Neutropenia: Guide for Healthcare Providers
 - Clozapine REMS Patient Enrollment Form
 - Clozapine REMS NC Lab Reporting Form
 - Important Safety Information
 - NC Calculator
 - NC Monitoring Table
- Wholesaler/Distributor
 - Contact the Clozapine REMS Program by sending an email to [A info@clozapinedistributor.com](mailto:info@clozapinedistributor.com)

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1 13 Prescribing Information .

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Prescribing Information

Products covered under the Clozapine REMS Program

Brand Name Products			
Trade Name	Generic Name	Company	Link

Generic Products			
Drug Name	Generic Name	Company	Link

The CPMG attests that the table above will only include products listed in the link titled "List of approved application numbers and sponsors" on the FDA Approved REMS Website.

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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. 4 Certification Lookup 1



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Certification Lookup

To search for a certified pharmacy, please complete at least one field below and press **Search**. Search results include contact information for pharmacies that are certified in the Clozapine REMS Program.

Pharmacy Information (at least one identifier is required):

or or or or

or and

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Certification Lookup

To search for a certified pharmacy, please complete at least one field below and press **Search**. Search results include contact information for pharmacies that are certified in the Clozapine REMS Program.

Pharmacy Information (at least one identifier is required):

or or or or

or and

Pharmacy Name	Certification ID	Pharmacy Address	Pharmacy Phone
Hogan Rx	FAC123456789	1234 W Scottsdale Rd. Scottsdale, AZ 85411	555-555-5555

Showing 1 of 1 entries

1 10

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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1 16 Site Map .

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Site Map

<p>Prescriber</p> <p>Prescriber Certification Prescriber FAQs Prescriber Resources Prescriber Support</p>	<p>Designee</p> <p>Prescriber Designee Certification Prescriber Designee Support</p> <p>Pharmacy Staff</p> <p>Pharmacy Staff Enrollment Pharmacy Staff Support</p> <p>General</p> <p>Contact Us General FAQs Important Safety Information Prescribing Information Privacy Professional Societies Resources Technical Support FAQs Terms of Use Wholesaler/Distributor FAQs Wholesaler/Distributor Resources</p>	<p>Account</p> <p>Forgot Password Forgot Username Need an Account</p>
<p>Pharmacy</p> <p>Pharmacy Certification Pharmacy FAQs Pharmacy Resources Pharmacy Support</p>		
<p>Patient</p> <p>Patient FAQs Patient Information Patient Resources Patient Support</p>		

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Frequently Asked Questions (FAQs)

- General**
- Patient
- Pharmacy
- Prescriber
- Technical Support
- Wholesaler/Distributor

- ▶ **What is the Clozapine REMS Program?**
- ▶ **What are the goals of the Clozapine REMS Program?**
- ▶ **What do I do if I am a user of one of the previous individual registries?**
- ▼ **How do I certify in the program?**

Stakeholders can be certified online through the Clozapine REMS Program website or by submitting the appropriate Prescriber, Pharmacy, or Designee Enrollment form via fax to the program contact center at 844-404-8876. To complete certification on the program website, from the Home page you will use the "Get Started" button. You will be taken to the applicable stakeholder certification page, which will explain what is expected and required of you from the Clozapine REMS Program. From that certification page, you can use the "Begin Now" button to start your certification in the program.
- ▶ **Who is a designee?**
- ▶ **How do I enroll my patient?**
- ▶ **What is the National Non-Rechallenge Master File (NNRMF)?**
- ▶ **How do I report patient lab ANC values?**
- ▶ **How do I report an adverse event, product complaint, or need medical information about clozapine?**
- ▶ **How can I find additional forms and program materials?**
- ▶ **How do I view and update my program profile?**
- ▶ **Will the program send me notices if my patient experiences a low ANC count or substantial drop?**
- ▶ **How do I contact the program?**

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Contact Us

If you have any questions or require additional information, please contact the Clozapine REMS Program utilizing the information provided below.

Phone Number
844-267-8678

Fax Number
844-404-8876

Mailing Address
Clozapine REMS Program
PO BOX 29058
PHOENIX AZ 85038-9058

Program Manufacturers

Company	Phone Number

The CPMG attests that the table above will only include products listed in the link titled "List of approved application numbers and sponsors" on the FDA Approved REMS Website."

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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2 User Identification and Record Search .

2 1 User Identification

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User Identification

Please select the option below that **best** describes you and press **Next**.

What type of user are you?

New User

Please choose your program role:

Authorized Representative for Pharmacy

Next

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Upon starting a rollme t or c rtificatio proc ss th us rs ar ask d to id tify what typ of us r th y ar what th ir rol is.

1 - Th optio s for typ of us r ar N w Us r, Pr vious gistry Us r, a d Pho /Fax Us r. Th tooltip xt to th fi ld will i clud a d fi itio of ach for th us r, which ar also b low.

- N w Us r – Us rs who ar w to clozapi a d ar ot part of a pr vious clozapi r gistry.
- Pr vious gistry Us r – Us rs who ar part of a pr vious clozapi r gistry
 - Th s us rs will s arch for th ir r cords a d start th rollme t or c rtificatio proc ss.
- Pho /Fax Us r – Us rs who submitt d a rollme t form through th co tact c tr via fax a d hav r c iv d a rollme t or c rtificatio ID.

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When the system locates the user's record and creates a web account, the user's web account and their enrollment or certification record are linked.

2 – The options for roles are Prescriber, Authorized Representative for Pharmacy, Prescriber or Designer, and Pharmacy Staff

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Previous Registry User Prescriber 2



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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Prescriber Information (at least one identifier is required):

<input type="text" value="First Name"/>	<input type="text" value="Last Name"/>	and	<input type="text" value="DEA"/>	or	<input type="text" value="NPI"/>
<input type="text" value="Phone (opt)"/>	<input type="text" value="Fax (opt)"/>	<input type="text" value="Email (opt)"/>			

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.3 Previous Registry User Prescriber Search with 2 Results



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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Prescriber Information (at least one identifier is required):

<input type="text" value="Summer"/>	<input type="text" value="Hogan"/>	and	<input type="text" value="AB12345789"/>	or	<input type="text" value="NPI"/>
<input type="text" value="Phone (opt)"/>	<input type="text" value="Fax (opt)"/>	<input type="text" value="Email (opt)"/>			

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, you can either try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Phone	DEA	NPI
Summer	Hogan	555-555-5555	AB1234567	

Showing 1 of 1 entries

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.4 Previous Registry User Prescriber Designee 2 Search

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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Prescriber Information

DEA

Designee Information

First Name Last Name

Phone (opt) Fax (opt) Email (opt)

[Search](#)

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Previous Registry User Precriber Designee Search with Results



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Previous Registry User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your registry status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Prescriber Information

Designee Information

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, you can either try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Phone
Summer	Hogan	555-555-5555

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2.6 Previous Registry User Pharmacy Search



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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

and or or

Authorized Representative Information

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Previous Registry User Pharmacy Search with Results



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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

and or or

Authorized Representative Information

First Name Last Name

Phone (opt) Fax (opt) Email (opt)

[Search](#)

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, you can either try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Pharmacy Name	Pharmacy Address	Pharmacy Phone
Summer	Hogan	Joey's Apothecary	1 Main Street, New York, NY 10001	555-555-5555

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[New User](#) [Submit](#)

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2.8 Pre-Registration User Pharmacy Staff Search



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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

and or or

Pharmacy Staff Information

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2.9 Pre-Registry User Pharmacy Staff Search with Results



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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information

Designee Information

[Search](#)

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, you can either try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Phone
Summer	Hogan	555-555-5555

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[New User](#) [Submit](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Previous Registry User Chain Pharmacy Headquarters 2

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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

Authorized Representative Information

[Search](#)

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Previous Registry User

If you are a user of any of the individual clozapine patient registries, your data may already be populated in the new Clozapine REMS Program. Please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

Authorized Representative Information

[Search](#)

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, please try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Pharmacy Name	Pharmacy Address	Phone
Summer	Hogan	Joey's Apothecary	1234 W Nowhere Lane Tempe, AZ 85283	555-555-5555

Showing 1 of 1 entries. 1 » 10

[New User](#) [Submit](#)

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Phone/Fax User Search

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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

At least one identifier below is required:

<input type="text" value="DEA"/>	<input type="text" value="NPI"/>	
<input type="text" value="First Name"/>	<input type="text" value="Last Name"/>	<input type="text" value="Certification ID (opt)"/>
<input type="text" value="Phone (opt)"/>	<input type="text" value="Fax (opt)"/>	<input type="text" value="Email (opt)"/>

[Search](#)

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Phone/Fax User Prescriber Search with Results

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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

At least one identifier below is required:

<input type="text" value="AB1234567"/>	<input type="text" value="NPI"/>	
<input type="text" value="Summer"/>	<input type="text" value="Hogan"/>	<input type="text" value="Certification ID (opt)"/>
<input type="text" value="Phone (opt)"/>	<input type="text" value="Fax (opt)"/>	<input type="text" value="Email (opt)"/>

[Search](#)

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, you can either try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Phone
Summer	Hogan	555-555-5555

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Phone/Fax User Prescriber Designee Search

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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Prescriber Information

Designee Information

[Search](#)

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2 15Phone Fax User Prescriber Designee Search with Results

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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Prescriber Information

Designee Information

[Search](#)

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, you can either try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Phone
Summer	Hogan	555-555-5555

Showing 1 of 1 entries 1 10

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Phone/Fax User Pharmacy Search



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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

<input type="text" value="Zip Code"/>	and	<input type="text" value="DEA"/>	<input type="text" value="NPI"/>	<input type="text" value="NCPDP"/>
---------------------------------------	-----	----------------------------------	----------------------------------	------------------------------------

Authorized Representative Information

<input type="text" value="First Name"/>	<input type="text" value="Last Name"/>	<input type="text" value="Certification ID (opt)"/>
<input type="text" value="Phone (opt)"/>	<input type="text" value="Fax (opt)"/>	<input type="text" value="Email (opt)"/>

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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

<input type="text" value="10001"/>	and	<input type="text" value="AB1234567890"/>	<input type="text" value="NPI"/>	<input type="text" value="NCPDP"/>
------------------------------------	-----	---	----------------------------------	------------------------------------

Authorized Representative Information

<input type="text" value="First Name"/>	<input type="text" value="Last Name"/>	<input type="text" value="Certification ID (opt)"/>
<input type="text" value="Phone (opt)"/>	<input type="text" value="Fax (opt)"/>	<input type="text" value="Email (opt)"/>

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, you can either try your search again or press the **New User** button to begin your certification process in the Clozapine REMS Program.

First Name	Last Name	Pharmacy Name	Pharmacy Address	Pharmacy Phone
Summer	Hogan	Joey's Apothecary	1 Main Street, New York, NY 10001	555-555-5555

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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information

Authorized Representative Information

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Phone/Fax User

If you began or completed certification through a fax process, you may already be certified in the Clozapine REMS Program. To determine your certification status, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information

Authorized Representative Information

[Search](#)

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, please try your search again or press the **New User** button to begin your enrollment process in the Clozapine REMS Program.

First Name	Last Name	Pharmacy Name	Pharmacy Address	Phone
Summer	Hogan	Joey's Apothecary	1234 W Nowhere Lane Tempe, AZ 85283	555-555-5555

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Web Account

.1 Create an Account 3



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Create an Account

Please complete the form below and press **Submit**. The information you provide for your Username must be unique within the Clozapine REMS Program website. Once you have submitted this form you will receive a verification email that includes a link. Please use the link to complete the activation process for your new web account. All fields below are required.

My Information

Account Type

First Name

Last Name

Email Address

Confirm Email Address

Phone Number


Sign in

Username

Use Email Address as Username

Password

Confirm Password

I'm not a robot 
reCAPTCHA
Privacy - Terms

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3.2 Account Verification 8

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Account Verification



A verification email has been sent to remsprogram@gmail.com.
Please use the link within the email to activate your web account for
the Clozapine REMS Program.

Account Summary

Name [Summer Hogan](#)

Email Address remsprogram@gmail.com

Phone Number [480-555-5555](tel:480-555-5555)

Username [summerhogan](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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3 3 Account Confirmation .

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Account Confirmation



✓ Your web account has been successfully activated. Please sign in to your account using the fields in the upper right corner of this page.

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4 prescriber Certification

4 1 Prescriber Intake

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Prescriber Intake

To certify as a prescriber in the Clozapine REMS Program, please complete the form below and press **Next**. Once certified, you will receive a certification confirmation via your contact preference. All fields listed below are required unless otherwise indicated.

Prescriber Information

First Name MI (opt)

Last Name

-- Credentials -- ▾

Email Address

Clinic / Practice Name

Address

Address 2 (opt)

City

-- State -- ▾ Zip Code

Phone Ext (opt)

Fax

-- Contact Preference -- ▾

Prescriber Identifiers

DEA

NPI

I do not have a DEA.

[Cancel](#) [Next](#)

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4 2 Prescriber Education Program.

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Education Program

Below is the education program for clozapine. Please review the program materials and press the **Next** button to continue. It is estimated that it will take 15 – 20 minutes to complete the Education Program and Knowledge Assessment.

Clozapine and the Risk of Neutropenia:
A Guide for Healthcare Providers

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1 The Clozapine REMS Program


Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/ μ L). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single, shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs, and is required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia.

The Clozapine REMS Program provides a **centralized** point of access:

1. For **prescribers** and **pharmacies** to certify before prescribing or dispensing clozapine
2. To enroll and manage **patients** on clozapine treatment

Clozapine is available by prescription as:

- Clozaril® (clozapine) tablets, for oral use
- Fazaclo® (clozapine, USP) orally disintegrating tablets
- Versacloz® (clozapine, USP) oral suspension
- Approved generic equivalents of these products

 **To minimize the risk of severe neutropenia associated with the use of clozapine, the Clozapine REMS Program includes the following key**

[Next](#)

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.3 Prescriber Education Confirmation 4

The screenshot displays the Clozapine REMS website interface. At the top left, the logo reads "CLOZAPINE REMS" with the tagline "The Single Shared System for Clozapine" and "No Blood, No Drug™". The user "Summer Hogan" is logged in, with a "My Dashboard" button. A navigation menu includes "Home", "Prescriber", "Pharmacy", "Patient", "Resources", "Important Safety Information", and "Support". A progress bar below the menu shows steps: Start, Intake, Education (highlighted), Assessment, Review, Attestation, and Finish. The main heading is "Education Program Confirmation". The text states: "You have now completed the Education Program". Below this, it says: "Please use the Next button below to continue with your certification process. The education program you just completed can always be reviewed again under your user profile in the top right corner of this site." A blue "Next" button is visible. At the bottom, a footer contains the text: "For additional information about the Clozapine REMS Program, please call 844-267-8678." and a link menu: "Privacy | Terms of Use | Site Map | FAQs | Contact Us".

Note: Upon pressing the Next button on the Education Confirmation page, the user will be navigated through the Knowledge Assessment. KA is shown only once below for all stakeholders except for **4** prescriber designees.

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Prescriber Intake Review4

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Prescriber Intake Review

Please review the information for completeness and accuracy. You may make any changes as necessary. When your review is complete, please use the **Next** button to save your information below and proceed to the final step in your certification process.

Prescriber Information

First Name / MI (opt)

Last Name

Credentials ▾

Email Address

Clinic / Practice Name

Address

Address 2 (opt)

City

State / Zip Code ▾

Phone / Ext (opt)

Fax

Contact Preference ▾

Prescriber Identifiers

DEA

NPI

I do not have a DEA.

[Cancel](#) [Next](#)

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4 5 Prescriber Attestation

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Start Intake Education Assessment Review **Attestation** Finish

Prescriber Attestation

To complete the prescriber certification for **Summer Hogan** into the Clozapine REMS Program online, please review the attestation section below to provide your acknowledgement along with signature and signature date.

Alternatively, you may print your online enrollment form using the print icon to the right and fax it to the Clozapine REMS Program at 844-404-8876. 

As a prescriber, I attest to the following Clozapine REMS Program requirements:

1. I understand that clozapine is only available through the Clozapine REMS Program and that I must comply with the program requirements to prescribe clozapine
2. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, reviewed the clozapine Prescribing Information, and successfully completed the *Knowledge Assessment for Healthcare Providers*
3. I understand the risk of severe neutropenia associated with clozapine
4. Prior to initiating treatment, I agree to provide *What You Need To Know About Clozapine: A Guide for Patients and Caregivers* to each patient and/or his/her caregiver. I will review it with him/her to inform them about the risks associated with clozapine, including severe neutropenia and the Clozapine REMS Program requirements – unless I determine that the patient's adherence to the treatment regimen will be negatively impacted by providing *What You Need To Know About Clozapine: A Guide for Patients and Caregivers*
5. I will enroll all patients I treat with a clozapine product in the Clozapine REMS Program
6. I understand the ANC testing and monitoring requirements as described in the clozapine Prescribing Information
7. I understand there is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
8. I will order ANC testing for each patient according to the clozapine Prescribing Information
9. I will report the ANC for each patient to the Clozapine REMS Program and I understand the ANC must be provided before clozapine can be dispensed
10. I understand that, as described in *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, I must authorize the continuation of clozapine treatment if the patient has moderate or severe neutropenia before clozapine can be dispensed
11. I agree that personnel from the Clozapine REMS Program may contact me to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
12. 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 Program
13. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Signature: Must match First and Last name (see above)

Signature Date

Back

Submit

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.6 Prescriber Confirmation 4

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Start Intake Education Assessment Review Attestation Finish

Certification Confirmation

✓ You are now certified in the Clozapine REMS Program.

Below is your Clozapine REMS Program Certification ID. Please retain this information for your records.

Certification ID: [HCP123456789](#) 🖨️

If you would like to enroll patients now you can use [Enroll Patient](#). If you need to manage your patients you can use [Manage Your Patients](#).

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Prescriber Designee Certification 5

.1 Prescriber Designee Intake

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Designee Intake

To certify as a designee in the Clozapine REMS Program, please complete the form below and press **Next**. Once certified, you will receive a certification confirmation via your contact preference. All fields listed below are required unless otherwise indicated.

Designee Information

[Cancel](#) [Next](#)

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5.2 Prescriber Designee Education Program Page 1

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General Information

Prescribers have the ability to identify and associate designees to their Clozapine REMS Program certification record. This allows prescribers the ability to approve responsible individual(s) to act on behalf of the certified prescriber for patients who are being treated with clozapine. Prescriber designees have the ability to provide ANC, and enroll and manage patients with the following exceptions:

- Designees cannot categorize a patient as diagnosed with BEN
- Designees cannot authorize the continuation of clozapine treatment for patients with moderate (General Population) or severe neutropenia (Patients with BEN)
- Designees cannot categorize a patient as a hospice patient.

[1](#) [2](#) [Next](#)

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Prescriber Designee Education Program Page 2

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Prescriber Designee Responsibilities

To be a designee for a certified prescriber in the Clozapine REMS Program, you must understand that you are acting on behalf of the certified prescriber, that clozapine is available only through the Clozapine REMS Program, and that you understand:

- Clozapine is only available through the Clozapine REMS Program and that I must comply with the program requirements
- There is a risk of severe neutropenia associated with clozapine
- The ANC testing and monitoring requirements as described in the clozapine Prescribing Information
- **For Outpatients:** An ANC must be reported to the Clozapine REMS Program for each patient, and I understand these results must be provided before clozapine can be dispensed
- **For Inpatients:** An ANC must be reported to the Clozapine REMS Program for each patient within 7 days from the date of blood draw
- To continue treatment with clozapine, the certified prescriber must provide a valid treatment rationale before clozapine can be dispensed to a patient, if the patient has moderate or severe neutropenia
- 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 Program
- Personnel from the Clozapine REMS Program may contact me to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
- I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

1 | 2

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Prescriber Designee Duration Confirmation

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Home **Prescriber** Pharmacy Patient Resources Important Safety Information Support

Start Intake **Education** Assessment Review Attestation Finish

Education Program Confirmation

You have now completed the **Education Program**

Please use the **Next** button below to continue with your certification process. The education program you just completed can always be reviewed again under your user profile in the top right corner of this site.

[Next](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Prescriber Description KA

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[Start](#) [Intake](#) [Education](#) **[Assessment](#)** [Review](#) [Attestation](#) [Finish](#)

Knowledge Assessment

Please select the **best** answer for the question. This question must be answered to proceed with the process to become certified in the program.

I have reviewed the requirements of the Clozapine REMS Program.

- A. Yes
- B. No

[Next](#)

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Prescriber Designee KA Confirmation – Success

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[Start](#) [Intake](#) [Education](#) [Assessment](#) [Review](#) [Attestation](#) [Finish](#)

Knowledge Assessment Results

✔ You have now completed the assessment.

You answered the question correctly and have passed the assessment. Please press the **Next** button to complete your certification.

Knowledge Assessment Confirmation Code: **1422-FEAF-BE87** 🖨️

I have reviewed the requirements of the Clozapine REMS Program.

✔ A. Yes

[Next](#)

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5 7 Pre cri er De ig ee KA Co firmatio – Not Successful

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[Start](#) [Intake](#) [Education](#) [Assessment](#) [Review](#) [Attestation](#) [Finish](#)

Knowledge Assessment Results

You did not pass the Knowledge Assessment.

Below is your response. Please use the **Retake Assessment** button to begin your assessment again.

I have reviewed the requirements of the Clozapine REMS Program.

✘ B. No

ATTEMPT

1	2	3	4	5	6
---	---	---	---	---	---

[Retake Assessment](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678

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5.8 Prescriber Designee Intake Review

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[Start](#) [Intake](#) [Education](#) [Assessment](#) [Review](#) [Attestation](#) [Finish](#)

Designee Intake Review

Please review the information below for completeness and accuracy. You may make any changes as necessary. When your review is complete please use the **Next** button to save your information below and proceed to the final step in your certification process.

Designee Information

First Name	<input type="text" value="Joe"/>
Last Name	<input type="text" value="Smith"/>
Email Address	<input type="text" value="jsmith@xyz.com"/>
Phone / Ext (opt)	<input type="text" value="555-555-5555"/> <input type="text" value="123"/>
Fax (opt)	<input type="text" value="Fax (opt)"/>
Contact Preference	<input type="text" value="Email"/>

[Cancel](#) [Next](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678

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Prescriber Designee Attestation

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Home **Prescriber** Pharmacy Patient Resources Important Safety Information Support

Start Intake Education Assessment Review **Attestation** Finish

Designee Attestation

To complete the designee certification for **Joe Smith** into the Clozapine REMS Program online, please review the attestation section below to provide your acknowledgement along with signature and signature date.

Alternatively, you may print your online enrollment form and fax it to the Clozapine REMS Program at 844-404-8876.

As a designee, I understand:

1. Clozapine is only available through the Clozapine REMS Program and that I must comply with the program requirements
2. There is a risk of severe neutropenia associated with clozapine
3. **For Outpatients:** An ANC must be reported to the Clozapine REMS Program for each patient, and I understand these results must be provided before clozapine can be dispensed
4. **For Inpatients:** An ANC must be reported to the Clozapine REMS Program for each patient within 7 days from the date of the blood draw
5. A certified prescriber must authorize the continuation of clozapine treatment, if the patient has moderate or severe neutropenia before clozapine can be dispensed to a patient
6. 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 Program
7. Personnel from the Clozapine REMS Program may contact me to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
8. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

By checking this box, I acknowledge that I will act on behalf of a certified prescriber to comply with the Clozapine REMS Program requirements. I hereby state that all of the information I have submitted is truthful and accurate.

Signature: Must match First and Last name (see above)

Signature Date

Back

Submit

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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5. 0Pre cri er De ig ee Co firmatio 5

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[Home](#) **Prescriber** [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

[Start](#) [Intake](#) [Education](#) [Assessment](#) [Review](#) [Attestation](#) [Finish](#)

Certification Confirmation

✔ You are now certified in the Clozapine REMS Program.

Below is your Clozapine REMS Program Certification ID. Please retain this information for your records.

Certification ID: [HCP123456789](#) 🖨️

If you are ready to associate yourself as a designee for a prescriber please go to the [Associate to Prescriber](#) page.

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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6. Pharmacy Certification 8

6.1 Role Selection

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Username Password [Sign in](#)
Forgot Username? Forgot Password? Need an Account?

[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Program Role Selection

Please select the option below that **best** describes your role and press **Continue**.

- Authorized Representative of Chain Pharmacy Headquarters** – An authorized representative of a chain pharmacy headquarters is responsible for ensuring certification and training in the Clozapine REMS Program for a corporate pharmacy contracted to participate with a pharmacy network provider. Corporate pharmacies are retail or mail outpatient pharmacy headquarters.
- Authorized Representative of Inpatient Pharmacy** – An authorized representative of an inpatient pharmacy is responsible for ensuring certification and training of the pharmacy staff within a pharmacy where the patient's treatment is coordinated at a site of care and pharmacy claims are submitted as a medical benefit.
- Authorized Representative of Outpatient Pharmacy** – An authorized representative of an outpatient pharmacy is responsible for ensuring certification and training of the pharmacy staff within an individual outpatient pharmacy. An authorized representative of an outpatient pharmacy cannot be affiliated with a chain pharmacy that is contracted with a pharmacy network provider.

[Continue](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.2 Role Selection Confirmation – Inpatient Pharmacy

The screenshot shows the Clozapine REMS website interface. At the top, there is a navigation bar with the logo and tagline, a search bar, and a 'Sign in' button. Below the navigation bar, there is a main content area with a 'Program Role Selection' section. A modal dialog box is open, titled 'Authorized Representative of Inpatient Pharmacy'. The dialog contains the following text:

Authorized Representative of Inpatient Pharmacy

Based on the response selected, please confirm you are certifying as an Inpatient Pharmacy.

An inpatient pharmacy is where the patient's treatment is coordinated at a site of care where pharmacy claims are submitted as a medical benefit.

If the pharmacy you are certifying does not meet the definition of an inpatient pharmacy, please press **Cancel** to change your response; otherwise, please press **Confirm** to continue with the certification.

At the bottom of the dialog are two buttons: 'Cancel' and 'Confirm'.

Below the dialog, there is a 'Continue' button and a footer with the text: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' At the very bottom, there is a footer with links: 'Privacy | Terms of Use | Site Map | FAQs | Contact Us'.

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6.3 Role Selection Confirmation – Outpatient Pharmacy

The screenshot displays the Clozapine REMS website interface. At the top, there is a navigation bar with the site logo, a login section (Username, Password, Sign in), and a menu (Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, Support). A central dialog box is overlaid on the page, titled "Authorized Representative of Outpatient Pharmacy". The dialog contains the following text:

Authorized Representative of Outpatient Pharmacy

Based on the response selected, please confirm that you are certifying as an **Outpatient Pharmacy**.

An outpatient pharmacy is a retail or institutional outpatient pharmacy not affiliated with any corporate pharmacy chain. The outpatient pharmacy has an authorized representative that is responsible for ensuring the education and training of pharmacy staff within the individualized location.

If the pharmacy you are certifying does not meet the definition of an outpatient pharmacy, please press **Cancel** to change your response; otherwise, please press **Confirm** to continue with the certification.

At the bottom of the dialog are two buttons: "Cancel" and "Confirm".

In the background, the "Program Role Selection" section is visible, with three radio button options for "Authorized Representative" roles. A "Continue" button is located below the options.

At the bottom of the page, there is a footer with the text: "For additional information about the Clozapine REMS Program, please call 844-267-8678." and a navigation bar with links for "Privacy", "Terms of Use", "Site Map", "FAQs", and "Contact Us".

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.4 Role Selection Confirmation – Chain Pharmacy 6 Headquarters

The screenshot displays the Clozapine REMS website interface. At the top, there is a navigation bar with the logo and tagline, a search bar, and a 'Sign in' button. Below the navigation bar, there are links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. The main content area is titled 'Program Role Selection' and contains a form with three radio button options. A modal dialog box is overlaid on the form, titled 'Authorized Representative of Chain Pharmacy Headquarters'. The dialog contains the following text: 'Based on the response selected, please confirm you are certifying as a Chain Pharmacy Headquarters'. Below this, it defines a chain pharmacy headquarters as a retail, mail order, or institutional outpatient pharmacy organization where a head office directs, coordinates and oversees a minimum of 10 outpatient pharmacies. It also provides instructions: 'If the pharmacy you are certifying does not meet the definition for a chain pharmacy headquarters, please press **Cancel** to change your response; otherwise, please press **Confirm** to continue with the certification.' At the bottom of the dialog are 'Cancel' and 'Confirm' buttons. The background form shows the first radio button option is selected. At the bottom of the page, there is a footer with the text 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' and a link to 'Privacy | Terms of Use | Site Map | FAQs | Contact Us'.

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Username Password Sign in
Forgot Username? Forgot Password? Need an Account?

Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Program Role Selection

Please select the option below that best describes your role:

- Authorized Representative of Chain Pharmacy Headquarters**
responsible for ensuring that all participating pharmacies in a pharmacy network participate in the program.
- Authorized Representative of Outpatient Pharmacy**
certification and training for participating pharmacies. Claims are submitted and managed through the program.
- Authorized Representative of Inpatient Pharmacy**
certification and training for participating pharmacies. Claims cannot be affiliated with the program.

Continue

Authorized Representative of Chain Pharmacy Headquarters

Based on the response selected, please confirm you are certifying as a Chain Pharmacy Headquarters

A chain pharmacy headquarters is a retail, mail order, or institutional outpatient pharmacy organization where a head office directs, coordinates and oversees a minimum of 10 outpatient pharmacies.

If the pharmacy you are certifying does not meet the definition for a chain pharmacy headquarters, please press **Cancel** to change your response; otherwise, please press **Confirm** to continue with the certification.

Cancel Confirm

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.5 Authorized Representative Intake 6

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[Home](#) [Prescriber](#) **[Pharmacy](#)** [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

[Intake](#) [Education](#) [Assessment](#) [Confirmation](#)

Authorized Representative Intake

To begin the process as an authorized representative in the Clozapine REMS Program, please complete the form below and press **Next**. All fields listed below are required unless otherwise indicated.

Authorized Representative Information

[Cancel](#) [Next](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Authorized Representative Confirmation 6

The screenshot shows the Clozapine REMS website interface. At the top left is the logo and tagline. The top right shows the user name 'Summer Hogan' and a 'My Dashboard' button. A navigation menu includes 'Home', 'Prescriber', 'Pharmacy', 'Patient', 'Resources', 'Important Safety Information', and 'Support'. Below the navigation is a progress bar with four steps: 'Intake', 'Education', 'Assessment', and 'Confirmation', with 'Confirmation' being the active step. The main content area is titled 'Confirmation' and features a green checkmark icon and a message box stating: 'You have successfully completed the required authorized representative training.' Below this message is a paragraph of instructions: 'If you are ready to certify your pharmacy now please use [Certify Pharmacy](#). To return to your dashboard for other activities, please use the **My Dashboard** button at the top of the page. If you have completed your session for today, simply close your browser.' At the bottom of the page, there is a footer with the text: 'For additional information about the Clozapine REMS Program, please call 1-844-267-8678.' and a secondary navigation bar with links for 'Privacy', 'Terms of Use', 'Site Map', 'FAQs', and 'Contact Us'.

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6.7 Pharmacy Intake

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[Home](#) [Prescriber](#) **[Pharmacy](#)** [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

[Intake](#) [Attestation](#) [Confirmation](#)

Pharmacy Intake

To certify your pharmacy, please complete the form below and press **Next**. Once certified, you will receive a certification confirmation via the contact preference you selected during your authorized representative intake. All fields listed below are required unless otherwise indicated.

Pharmacy Information

Pharmacy Name

Pharmacy Type ?

Address

Address 2 (opt)

City

-- State -- Zip Code

Phone Ext (opt)

Fax

Pharmacy Identifiers

NCPDP

DEA (opt)

NPI

Can your pharmacy management system adjudicate claims online?

-- Please Select -- **1**

[Cancel](#) [Next](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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1 – Adjudicate claims online question – This question will be displayed only if the Pharmacy Type selected on this page is ‘Outpatient Pharmacy’.

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6.8 Pharmacy Education Program⁸

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[Intake](#) **[Education](#)** [Assessment](#) [Confirmation](#)

Education Program

Below is the education program for clozapine. Please review the program materials and press the **Next** button to continue. It is estimated that it will take 15 – 20 minutes to complete the Education Program and Knowledge Assessment.

Clozapine and the Risk of Neutropenia:
A Guide for Healthcare Providers

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1 The Clozapine REMS Program


Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/ μ L). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single, shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs, and is required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia.

The Clozapine REMS Program provides a **centralized** point of access:

1. For **prescribers** and **pharmacies** to certify before prescribing or dispensing clozapine
2. To enroll and manage **patients** on clozapine treatment

Clozapine is available by prescription as:

- Clozaril® (clozapine) tablets, for oral use
- Fazaclo® (clozapine, USP) orally disintegrating tablets
- Versacloz® (clozapine, USP) oral suspension
- Approved generic equivalents of these products

 **To minimize the risk of severe neutropenia associated with the use of clozapine, the Clozapine REMS Program includes the following key**

[Next](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.9 Pharmacy Education Confirmation 6

The screenshot displays the Clozapine REMS website interface. At the top left, the logo 'CLOZAPINE REMS' is shown with the tagline 'The Single Shared System for Clozapine' and 'No Blood, No Drug™'. In the top right corner, the user name 'Summer Hogan' and a 'My Dashboard' button are visible. A navigation menu below the logo includes links for 'Home', 'Prescriber', 'Pharmacy' (highlighted), 'Patient', 'Resources', 'Important Safety Information', and 'Support'. A secondary navigation bar contains buttons for 'Intake', 'Education' (highlighted), 'Assessment', and 'Confirmation'. The main heading is 'Education Program Confirmation'. Below this, a message states: 'You have now completed the Education Program'. A paragraph of text follows: 'Please use the Next button below to continue with your certification process. The education program you just completed can always be reviewed again under your user profile in the top right corner of this site.' A blue 'Next' button is positioned below the text. At the bottom of the page, a footer contains the text: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' and a secondary navigation bar with links for 'Privacy', 'Terms of Use', 'Site Map', 'FAQs', and 'Contact Us'.

Note: Upon pressing the Next button on the Education Confirmation page, the user will be navigated through the Knowledge Assessment. KA is shown only once below for all stakeholders except for **6** prescriber designees.

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6.10 Pharmacy Attestation – Inpatient Pharmacy

This page includes only the attestation text for the Inpatient Pharmacy from the Clozapine REIMS Pharmacy Enrollment Form.

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Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Intake Attestation **Confirmation**

Pharmacy Attestation

To complete the certification for <Pharmacy Name> into the Clozapine REIMS Program online, please review the attestation section below to provide your acknowledgement along with signature and signature date.

Alternatively, you may print your online enrollment form using the print icon to the right and fax it to the Clozapine REIMS Program at 844-404-8676. 

As an authorized representative responsible for the pharmacy, I, **Summer Hogan**, attest to the following Clozapine REIMS Program requirements:

I am the authorized representative designated by my pharmacy to coordinate the activities of the Clozapine REIMS Program. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and the Prescribing Information and I understand:

1. Pharmacies must certify in the Clozapine REIMS Program to order and dispense clozapine
2. The risk of severe neutropenia associated with clozapine and the importance of ANC monitoring
3. There is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
4. Clozapine manufacturers, their agents and contractors may contact me to obtain names of our pharmacists to survey on the effectiveness of the program requirements for the Clozapine REIMS Program

On behalf of the pharmacy, I agree to comply with the following program requirements:

5. My pharmacy will establish procedures and protocols that are subject to audit, to help ensure compliance with the requirements of the Clozapine REIMS Program, including the following before dispensing clozapine:
 - All pharmacists and relevant staff involved in dispensing clozapine are trained and a record of the training is maintained
 - Verify the prescriber is certified and the patient is enrolled in the Clozapine REIMS Program
 - Verify the ANC is current and acceptable or verify the prescriber's authorization for continuing clozapine treatment if the ANC is abnormal
 - Fill and dispense no more than the amount of clozapine necessary to treat the patient until the next blood draw/ANC or as directed by the prescriber
6. My pharmacy will establish procedures and protocols that are subject to audit, to not sell, loan, or transfer any clozapine inventory to any other pharmacy institution, distributor, or prescriber that is not enrolled in the Clozapine REIMS Program
7. Pharmacies will renew enrollment in the Clozapine REIMS Program every two years to maintain certification to order and dispense clozapine
8. Pharmacies will make available to the clozapine manufacturers and/or a designated third party or the FDA, documentation to verify understanding of, and adherence to, the requirements of the Clozapine REIMS Program
9. Clozapine REIMS Program personnel may contact my pharmacists to gather information or resolve discrepancies or to provide other information related to the Clozapine REIMS Program
10. Provide dispensing location information to the Clozapine REIMS Program
11. I will not share my credentials for the Clozapine REIMS Program website or allow others to sign into the website using my credentials
12. Inpatient pharmacies are not required to obtain a Predispose Authorization (PDA) prior to dispensing clozapine.

Before dispensing clozapine to an inpatient for the first time, the inpatient pharmacies must:

- Verify the prescriber is certified in the Clozapine REIMS Program
- Verify the patient is enrolled in the Clozapine REIMS Program

Before dispensing clozapine to an inpatient for the first time, the inpatient pharmacies must:

1. Sign in into the Clozapine REIMS Program website at www.clozapinerems.com, or
2. Call the Clozapine REIMS Program contact center at 844-267-8678

Inpatient pharmacies must verify the ANC or prescriber's authorization for a patient to continue clozapine treatment in one of three ways:

1. By signing into the Clozapine REIMS Program website at www.clozapinerems.com
2. By calling the Clozapine REIMS Program contact center at 844-267-8678
3. By reviewing the patient's medical record in their hospital's medical record system

Prescribers or their designee(s) must submit ANC to the Clozapine REIMS Program within 7 days of blood draw.

By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Signature: Must match First and Last name (see above) Signature Date

For additional information about the Clozapine REIMS Program, please call 844-267-8678.

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Pharmacy Attestation – Outpatient Pharmacy

This page includes only the attestation text for the Outpatient Pharmacy from the Clozapine REMS Pharmacy Enrollment Form. **6**

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Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Intake **Attestation** Confirmation

Pharmacy Attestation

To complete the certification for <Pharmacy Name> into the Clozapine REMS Program online, please review the attestation section below to provide your acknowledgement along with signature and signature date.

Alternatively, you may print your online enrollment form using the print icon to the right and fax it to the Clozapine REMS Program at 844-404-8876. 

As an authorized representative responsible for the pharmacy, I, **Summer Hogan**, attest to the following Clozapine REMS Program requirements:

I am the authorized representative designated by my pharmacy to coordinate the activities of the Clozapine REMS Program. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and the Prescribing Information and I understand:

1. Pharmacies must certify in the Clozapine REMS Program to order and dispense clozapine
2. The risk of severe neutropenia associated with clozapine and the importance of ANC monitoring
3. There is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
4. Clozapine manufacturers, their agents and contractors may contact me to obtain names of our pharmacists to survey on the effectiveness of the program requirements for the Clozapine REMS Program

On behalf of the pharmacy, I agree to comply with the following program requirements:

5. My pharmacy will establish procedures and protocols that are subject to audit, to help ensure compliance with the requirements of the Clozapine REMS Program, including the following before dispensing clozapine:
 - All pharmacists and relevant staff involved in dispensing clozapine are trained and a record of the training is maintained
 - Verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program
 - Verify the ANC is current and acceptable or verify the prescriber's authorization for continuing clozapine treatment if the ANC is abnormal
 - Fill and dispense no more than the amount of clozapine necessary to treat the patient until the next blood draw/ANC or as directed by the prescriber
6. My pharmacy will establish procedures and protocols that are subject to audit, to not sell, loan, or transfer any clozapine inventory to any other pharmacy institution, distributor, or prescriber that is not enrolled in the Clozapine REMS Program
7. Pharmacies will renew enrollment in the Clozapine REMS Program every two years to maintain certification to order and dispense clozapine
8. Pharmacies will make available to the clozapine manufacturers and/or a designated third party or the FDA, documentation to verify understanding of, and adherence to, the requirements of the Clozapine REMS Program
9. Clozapine REMS Program personnel may contact my pharmacists to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
10. Provide dispensing location information to the Clozapine REMS Program
11. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials
12. Outpatient Pharmacies must obtain a Predispose Authorization (PDA) before dispensing clozapine products to a patient to ensure compliance with the required safe use conditions. You are confirming that your pharmacy management system CANNOT support electronic communication with the Clozapine REMS Program and you will access the Clozapine REMS Program website or call the Clozapine REMS Program contact center to confirm safe use conditions (as outlined in attestation #5) before dispensing each clozapine prescription. A complete Predispose Authorization request requires the pharmacist to identify a unique patient, provide dispense information, and provide the prescriber's NPI or DEA.

By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Signature: Must match First and Last name (see above) Signature Date

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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2 Pharmacy Attestation – Outpatient Pharmacy with Adjudication

This page includes only the attestation text for the Outpatient Pharmacy from the Clozapine REMS Pharmacy Enrollment Form.

Summer Hogan ▾ My Dashboard

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Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Intake **Attestation** Confirmation

Pharmacy Attestation

To complete the certification for <Pharmacy Name> into the Clozapine REMS Program online, please review the attestation section below to provide your acknowledgement along with signature and signature date.

Alternatively, you may print your online enrollment form using the print icon to the right and fax it to the Clozapine REMS Program at 844-404-8876. 

As an authorized representative responsible for the pharmacy, I, **Summer Hogan**, attest to the following Clozapine REMS Program requirements:

I am the authorized representative designated by my pharmacy to coordinate the activities of the Clozapine REMS Program. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and the Prescribing Information and I understand:

1. Pharmacies must certify in the Clozapine REMS Program to order and dispense clozapine
2. The risk of severe neutropenia associated with clozapine and the importance of ANC monitoring
3. There is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
4. Clozapine manufacturers, their agents and contractors may contact me to obtain names of our pharmacists to survey on the effectiveness of the program requirements for the Clozapine REMS Program

On behalf of the pharmacy, I agree to comply with the following program requirements:

5. My pharmacy will establish procedures and protocols that are subject to audit, to help ensure compliance with the requirements of the Clozapine REMS Program, including the following before dispensing clozapine:
 - All pharmacists and relevant staff involved in dispensing clozapine are trained and a record of the training is maintained
 - Verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program
 - Verify the ANC is current and acceptable or verify the prescriber's authorization for continuing clozapine treatment if the ANC is abnormal
 - Fill and dispense no more than the amount of clozapine necessary to treat the patient until the next blood draw/ANC or as directed by the prescriber
6. My pharmacy will establish procedures and protocols that are subject to audit, to not sell, loan, or transfer any clozapine inventory to any other pharmacy institution, distributor, or prescriber that is not enrolled in the Clozapine REMS Program
7. Pharmacies will renew enrollment in the Clozapine REMS Program every two years to maintain certification to order and dispense clozapine
8. Pharmacies will make available to the clozapine manufacturers and/or a designated third party or the FDA, documentation to verify understanding of, and adherence to, the requirements of the Clozapine REMS Program
9. Clozapine REMS Program personnel may contact my pharmacists to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
10. Provide dispensing location information to the Clozapine REMS Program
11. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials
12. Outpatient Pharmacies must obtain a Predispose Authorization (PDA) before dispensing clozapine products to a patient to ensure compliance with the required safe use conditions. You are confirming that your pharmacy management system CAN support electronic communication with the Clozapine REMS Program using established telecommunications standards. Clozapine will be dispensed only after obtaining electronic authorization for all clozapine prescriptions, including cash claims, through your pharmacy management system. As part of your certification process, you will receive instructions through the contact preference indicated in the authorized representative information section on how to submit test transactions to the Clozapine REMS Program. This is to ensure that your pharmacy management system has been successfully configured to allow for communication with the Clozapine REMS Program.

By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Signature: Must match First and Last name (see above) Signature Date

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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6.13 Pharmacy Confirmation

This page will be available for:

1. Inpatient Pharmacies
2. Outpatient Pharmacies who cannot adjudicate claims online 8

The screenshot shows the Clozapine REMS website interface. At the top left is the logo 'CLOZAPINE REMS' with the tagline 'The Single Shared System for Clozapine' and 'No Blood, No Drug™'. To the right of the logo is the user name 'Summer Hogan' and a 'My Dashboard' button. Below the logo is a navigation menu with links for 'Home', 'Prescriber', 'Pharmacy' (highlighted), 'Patient', 'Resources', 'Important Safety Information', and 'Support'. A secondary navigation bar contains three buttons: 'Intake', 'Attestation', and 'Confirmation'. The main heading is 'Certification Confirmation' with a decorative graphic of colored squares. A green-bordered box contains a checkmark and the text: 'Your pharmacy is now certified in the Clozapine REMS Program.' Below this, a message states: 'Below is your Clozapine REMS Program Certification ID. Please retain this information for your records.' The certification ID is displayed as 'FAC123456789' with a copy icon. A note follows: 'To add additional pharmacies or manage your pharmacies, please use the My Dashboard button at the top of the page.' Another note says: 'Please download the Education Program, Knowledge Assessment, and Knowledge Assessment Answer Guide from your Profile page. These tools should be used to train all pharmacists and relevant staff involved in dispensing clozapine. A record of the training must be maintained for future review by the Clozapine REMS Program.' At the bottom, a call to action reads: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' The footer contains links for 'Privacy', 'Terms of Use', 'Site Map', 'FAQs', and 'Contact Us'.

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6 14 Pharmacy Test Transactions

This page will be available for:

1. Outpatient Pharmacies who can adjudicate claims online .
2. Chain Pharmacy Headquarters

Summer Hogan ▾ My Dashboard

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Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Intake Attestation Confirmation


Pharmacy Test Transactions

✔ Thank you! Your enrollment form was successfully submitted.

To complete the final step in your certification process, you must now successfully perform a software validation test to verify your pharmacy management system. This will ensure that your pharmacy management system has been successfully configured to allow communication with the Clozapine REMS Program.

You will soon receive a communication via your contact preference with instructions on how to submit test transactions to the Clozapine REMS Pharmacy Program.

To download the instructions now, please use the **Download Instructions** link below. After successful completion of the test transactions and validation of all required identifiers, you will be notified of your certification in the Clozapine REMS Program through your contact preference.

 [Download Instructions](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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7 Chain Pharmacy Certification

7.1 Chain Headquarters Identification .

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Username Password [Sign in](#)
[Forgot Username?](#) [Forgot Password?](#) [Need an Account?](#)

[Home](#) [Prescriber](#) **[Pharmacy](#)** [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Chain Headquarters Identification

Please enter the REMS Chain ID assigned to your chain below and press **Search**. If you do not know your REMS Chain ID please contact the Clozapine REMS Program at 844-267-8678.

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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7 2 Chain Headquarters Identification Results .

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Username Password [Sign in](#)
[Forgot Username?](#) [Forgot Password?](#) [Need an Account?](#)

[Home](#) [Prescriber](#) **[Pharmacy](#)** [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Chain Headquarters Identification

Please enter the REMS Chain ID assigned to your chain below and press **Search**. If you do not know your REMS Chain ID please contact the Clozapine REMS Program at 844-267-8678.

[Search](#)

The chain headquarters associated with the REMS Chain ID provided is participating in the Clozapine REMS Program. Press **Next** to continue.

[Next](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.3 Chain Authorized Representative Intake 7

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[Intake](#) [Education](#) [Assessment](#) [Confirmation](#)

Authorized Representative Intake

To begin the process as an authorized representative in the Clozapine REMS Program, please complete the form below and press **Next**. All fields listed below are required unless otherwise indicated.

Authorized Representative Information

▾

▾

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.4 Chain Pharmacy Education Program7

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Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Intake Education Assessment Confirmation

Education Program

Below is the education program for clozapine. Please review the program materials and press the **Next** button to continue. It is estimated that it will take 15 – 20 minutes to complete the Education Program and Knowledge Assessment.

Clozapine and the Risk of Neutropenia:
A Guide for Healthcare Providers

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3

1 The Clozapine REMS Program


Clozapine is associated with severe neutropenia (absolute neutrophil count (ANC) less than 500/ μ L). The requirements to prescribe, dispense, and receive clozapine are incorporated into a single, shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. A REMS is a strategy to manage known or potential risks associated with a drug or group of drugs, and is required by the FDA for clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia.

The Clozapine REMS Program provides a **centralized** point of access:

1. For **prescribers** and **pharmacies** to certify before prescribing or dispensing clozapine
2. To enroll and manage **patients** on clozapine treatment

Clozapine is available by prescription as:

- Clozaril® (clozapine) tablets, for oral use
- Fazaclo® (clozapine, USP) orally disintegrating tablets
- Versacloz® (clozapine, USP) oral suspension
- Approved generic equivalents of these products

 **To minimize the risk of severe neutropenia associated with the use of clozapine, the Clozapine REMS Program includes the following key**

Next

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7.5 Chain Pharmacy Education Confirmation

The screenshot shows the Clozapine REMS website interface. At the top left is the logo and tagline. On the top right, the user name 'Summer Hogan' and a 'My Dashboard' button are visible. A navigation menu includes 'Home', 'Prescriber', 'Pharmacy', 'Patient', 'Resources', 'Important Safety Information', and 'Support'. Below the menu is a progress bar with steps: 'Start', 'Intake', 'Education' (highlighted), 'Assessment', 'Review', 'Attestation', and 'Finish'. The main heading is 'Education Program Confirmation'. The text states: 'You have now completed the Education Program'. Below this, it says: 'Please use the Next button below to continue with your certification process. The education program you just completed can always be reviewed again under your user profile in the top right corner of this site.' A blue 'Next' button is positioned below the text. At the bottom of the page, there is a footer with the text: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' and a navigation bar with links for 'Privacy', 'Terms of Use', 'Site Map', 'FAQs', and 'Contact Us'.

Note: Upon pressing the Next button on the Education Confirmation page, the user will be navigated through the Knowledge Assessment. KA is shown only once below for all stakeholders except for prescriber designees.

Note: Attestation will occur at the pharmacy level during the Certify Headquarters process.

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.6 Chain Authorized Representative Confirmation 7

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[Intake](#) [Education](#) [Assessment](#) [Confirmation](#)

Confirmation



✓ You have successfully completed the required authorized representative training.

If you are ready to enroll your headquarters now please use [Certify Headquarters](#). If you have completed your session for today, simply close your browser.

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Chain Pharmacy Headquarters Intake

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[Intake](#) [Attestation](#) [Confirmation](#)

Chain Pharmacy Headquarters Intake

To certify your headquarters, please complete the form below and press **Next**. Once certified, you will receive a certification confirmation via the contact preference you selected during your authorized representative intake. All fields listed below are required unless otherwise indicated.

Headquarters Information

<input type="text" value="Chain Name"/>
<input type="text" value="Address"/>
<input type="text" value="Address 2 (opt)"/>
<input type="text" value="City"/>
<input type="text" value="-- State --"/> <input type="text" value="Zip Code"/>
<input type="text" value="Phone"/> <input type="text" value="Ext (opt)"/>
<input type="text" value="Fax"/>

[Cancel](#) [Next](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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7 8 Chain Pharmacy Headquarters Attestation .

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Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Intake Attestation Confirmation

Chain Pharmacy Headquarters Attestation

To complete the certification for **Rite Aid** into the Clozapine REMS Program online, please review the attestation section below to provide your acknowledgement along with signature and signature date.

Alternatively, you may print your online enrollment form and fax it to the Clozapine REMS Program at 844-404-8876. 

As the authorized representative responsible for this chain headquarters, I, **Summer Hogan**, attest to the following Clozapine REMS program requirements:

I am the authorized representative designated by this chain headquarters to coordinate the activities of the Clozapine REMS Program. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, the Prescribing Information, and I understand:

- Pharmacies must certify in the Clozapine REMS Program to order and dispense clozapine
- The risk of severe neutropenia associated with clozapine and the importance of ANC monitoring
- There is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
- Clozapine manufacturers, their agents and contractors may contact me to obtain names of our pharmacists to contact them via phone, mail, or email to survey on the effectiveness of the program requirements for the Clozapine REMS Program

On behalf of the pharmacy, I agree to comply with the following program requirements:

1. My pharmacy will establish procedures and protocols that are subject to audit, to help ensure compliance with the safe use conditions required in the Clozapine REMS Program, including the following, before dispensing clozapine:
 - All pharmacists and relevant staff involved in dispensing clozapine are trained and a record of the training is maintained
 - Through electronic communication with the Clozapine REMS Program using established telecommunications standards, my pharmacy will dispense clozapine to each patient only after obtaining authorization by electronically verifying documentation of the following:
 - Prescriber is certified in the Clozapine REMS Program
 - Pharmacy is certified in the Clozapine REMS Program
 - Patient is enrolled in the Clozapine REMS Program
 - The ANC is current and acceptable or the prescriber has authorized continuing treatment if the ANC is abnormal
 - This information will be verified by processing all clozapine prescriptions, including cash claims, through the pharmacy management system
 - Fill and dispense no more than the amount of clozapine necessary to treat the patient until the next blood draw/ANC or as directed by the prescriber
2. My pharmacy agrees not to sell, loan, or transfer any clozapine inventory to any other pharmacy institution, distributor, or prescriber that is not enrolled in the Clozapine REMS Program, and will establish procedures and protocols to support these requirements that are subject to audit
3. Pharmacies will renew enrollment in the Clozapine REMS Program every two years to maintain certification to order and dispense clozapine.
4. Pharmacies will make documentation available to the clozapine manufacturers and/or a designated third party or the FDA to verify understanding of, and adherence to, the requirements of the Clozapine REMS Program
5. Clozapine REMS Program personnel may contact pharmacists in my pharmacy to gather information, resolve discrepancies, or to provide other information related to the Clozapine REMS Program
6. For each trained dispensing location provide the following information (Pharmacy Name, NCPDP or NPI or DEA, Address, Phone, Fax, Email, Store Number, and Responsible Pharmacist name)
7. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Signature: Must match First and Last name (see above)

Signature Date

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Submit

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.9 Pharmacy Test Transactions

At this point in the chain pharmacy process, the authorized representative must complete test transactions prior to being "Certified" in the program. Once they finish the test transactions they will have the ability to access their Dashboard page and add a chain store. 7

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Summer Hogan ▾ My Dashboard

Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Intake Attestation Confirmation


Pharmacy Test Transactions

✓ Thank you! Your enrollment form was successfully submitted.

To complete the final step in your certification process, you must now successfully perform a software validation test to verify your pharmacy management system. This will ensure that your pharmacy management system has been successfully configured to allow communication with the Clozapine REMS Program.

You will soon receive a communication via your contact preference with instructions on how to submit test transactions to the Clozapine REMS Pharmacy Program.

To download the instructions now, please use the **Download Instructions** link below. After successful completion of the test transactions and validation of all required identifiers, you will be notified of your certification in the Clozapine REMS Program through your contact preference.

 [Download Instructions](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.10Chain Pharmacy Store Intake 7

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Chain Pharmacy Store Intake

To certify your chain pharmacy store, please complete the form below and press **Next**. Once the store is certified, you will receive a certification confirmation via the contact preference you selected during your authorized representative intake. All fields below are required unless otherwise indicated.

Pharmacy Information

Pharmacy Name

Address

Address 2 (opt)

City

-- State -- ▾

Phone Ext (opt)

Fax

--Training Status-- ▾

Pharmacy Identifiers

NCPDP

Please provide at least one:

DEA

NPI

[Cancel](#) [Submit](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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.11 Chain Pharmacy Store Confirmation 7

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Chain Store Confirmation

✓ The chain pharmacy store has been successfully added.

To add another store, please use the **Add Store** button below.

[Add Store](#) [My Dashboard](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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Pharmacy Staff Enrollment 8

.1 Pharmacy Search

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[Start](#) [Intake](#) [Attestation](#) [Finish](#)

Pharmacy Search

To identify the pharmacy you represent, please complete the fields below and press **Search**. Once you are able to access your dashboard, you will be able to associate to additional pharmacies. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

<input type="text" value="Zip Code"/>	and	<input type="text" value="DEA"/>	<input type="text" value="NPI"/>	<input type="text" value="NCPDP"/>
---------------------------------------	-----	----------------------------------	----------------------------------	------------------------------------

[Search](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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8.2 Pharmacy Search Results 8

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[Start](#) [Intake](#) [Attestation](#) [Finish](#)

Pharmacy Search

To identify the pharmacy you represent, please complete the fields below and press **Search**. Once you are able to access your dashboard, you will be able to associate to additional pharmacies. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

<input type="text" value="10001"/>	and	<input type="text" value="DEA"/>	<input type="text" value="NPI"/>	<input type="text" value="3456789"/>
------------------------------------	-----	----------------------------------	----------------------------------	--------------------------------------

[Search](#)

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, please try your search again or contact the Clozapine REMS Program for assistance.

Pharmacy Name	Pharmacy Address	Pharmacy Phone
CVS	423 Main Street, Tampa FL 33614	555-555-5555

Showing 1 of 1 entries

[Submit](#)

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8.3 Pharmacy Staff Intake 8

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[Start](#) **[Intake](#)** [Attestation](#) [Finish](#)

Pharmacy Staff Intake

To enroll as a pharmacy staff in the Clozapine REMS Program, please complete the form below and press **Next**. Once enrolled, you will receive an enrollment confirmation via your contact preference. All fields listed below are required unless otherwise indicated.

Pharmacy Staff Information

▾

[Cancel](#) [Next](#)

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.4 Pharmacy Staff Attestation 8

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Home Prescriber **Pharmacy** Patient Resources Important Safety Information Support

Start Intake **Attestation** Finish

Pharmacy Staff Attestation

To complete the pharmacy staff enrollment for **Summer Hogan** into the Clozapine REMS Program online, please review the attestation section below to provide your acknowledgement along with signature and signature date.

As a pharmacy staff, I attest to the following Clozapine REMS Program requirements:

Pharmacy Staff can access the Clozapine REMS Program online to do the following:

- Enter an ANC for a patient
- Verify a prescriber is certified in the Clozapine REMS Program
- Verify a patient is enrolled in the Clozapine REMS Program
- Obtain a Predispose Authorization (PDA) (Inpatient Pharmacies do not have to obtain a PDA)

For online access to perform the above tasks, you must enroll by creating an account.

By enrolling, you agree not to share your credentials for the Clozapine REMS Program website or allow others to sign into the website using your credentials.

As part of your enrollment, you must select the certified pharmacy location(s) where you fill and/or dispense clozapine. It is your responsibility to update this information as necessary.

By checking this box, I hereby state that all of the information I have submitted is truthful and accurate.

Signature: Must match First and Last name (see above)

Signature Date

Back

Submit

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8.5 Pharmacy Staff Confirmation 8

The screenshot shows the Clozapine REMS website interface. At the top left is the logo and tagline. The top right shows the user name 'Summer Hogan' and a 'My Dashboard' button. A navigation menu includes 'Home', 'Prescriber', 'Pharmacy' (highlighted), 'Patient', 'Resources', 'Important Safety Information', and 'Support'. Below the navigation is a progress bar with buttons for 'Start', 'Intake', 'Attestation', and 'Finish'. The main heading is 'Enrollment Confirmation'. A green checkmark icon is followed by the text 'You have now enrolled in the Clozapine REMS Program.' Below this, a message states: 'Below is your Clozapine REMS Program Enrollment ID. Please retain this information for your records.' The enrollment ID is displayed as 'HCP123456789'. A final instruction reads: 'To return to your dashboard for other activities, please use the My Dashboard button at the top of the page. If you have completed your session for today, simply close your browser.' At the bottom, a footer contains the text: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' and a navigation bar with links for 'Privacy', 'Terms of Use', 'Site Map', 'FAQs', and 'Contact Us'.

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9K Knowledge Assessment

The Knowledge Assessment pages below are for prescribers, prescriber designees, and authorized representatives.

9.1 Knowledge Assessment Landing Page 8

The screenshot shows the user interface for the Clozapine REMS Knowledge Assessment. At the top left is the logo for Clozapine REMS, "The Single Shared System for Clozapine, No Blood, No Drug™". To the right of the logo is the user's name, "Summer Hogan", and a "My Dashboard" button. Below the logo is a navigation menu with links for Home, Prescriber (highlighted), Pharmacy, Patient, Resources, Important Safety Information, and Support. A secondary navigation bar contains buttons for Start, Intake, Education, Assessment (highlighted), Review, Attestation, and Finish. The main heading is "Knowledge Assessment". The text below explains that the user will review questions to test their knowledge of clozapine use and administration, and that they must answer all questions correctly. It also states that there are six attempts to pass the assessment, and that after three unsuccessful attempts, the education program must be reviewed, and after six, access to retake the assessment will be suspended. A "Start Assessment" button is centered on the page. At the bottom, there is a call to action: "For additional information about the Clozapine REMS Program, please call 844-267-8678." The footer contains links for Privacy, Terms of Use, Site Map, FAQs, and Contact Us.

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Knowledge Assessment 9

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Knowledge Assessment

QUESTION 1

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

- A. True
- B. False

Next

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QUESTION 2

Clozapine is associated with severe neutropenia.

- A. True
- B. False

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Knowledge Assessment

QUESTION 3

Severe neutropenia is defined as:

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

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Knowledge Assessment

QUESTION 4

Before initiating treatment with clozapine:

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

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Knowledge Assessment

QUESTION 5

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

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

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Knowledge Assessment

QUESTION 6

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

- A. True
- B. False

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Knowledge Assessment

QUESTION 7

Before clozapine can be dispensed, a pharmacist must:

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

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Knowledge Assessment

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

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QUESTION 9

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

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

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Knowledge Assessment

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

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Knowledge Assessment

QUESTION 11

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

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

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Knowledge Assessment

QUESTION 12

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

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

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Knowledge Assessment

QUESTION 13

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

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

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Intake Education Assessment **Confirmation**

Knowledge Assessment Results

✓ You have now completed the assessment.

You answered all the questions correctly and have passed the assessment. Please press the **Next** button to complete your certification.

Knowledge Assessment Code: **1422-FEAF-BE87** 🖨️

QUESTION 1

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

✓ A. True

QUESTION 2

Clozapine is associated with severe neutropenia.

✓ A. True

Next

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Intake Education Assessment **Confirmation**

Knowledge Assessment Results

You did not pass the Knowledge Assessment.

Below is a summary of your responses. We recommend you review the Education Program again before you attempt to retake the Knowledge Assessment. Once you feel your review is complete, please use the **Retake Assessment** button below to begin your assessment again.

QUESTION 1

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

✓ A. True

QUESTION 2

Clozapine is associated with severe neutropenia.

✗ A. False

ATTEMPT
1 2 3 4 5 6

Retake Assessment

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0. Patient Enrollment 1

0. Patient Intake

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[Start](#) [Intake](#) [Lab Info](#) [Finish](#)

Patient Intake

To enroll your patient in the Clozapine REMS Program, please complete the form below and press **Next**. Once the patient enrollment is complete, you will receive an enrollment confirmation via your contact preference. All fields listed below are required.

Patient Information

First Name

Last Name

Date of Birth (MM/DD/YYYY)

Zip Code

-- Gender -- ▾

-- Race -- ▾

-- Patient Group -- ▾ [?](#)

Does the patient have Benign Ethnic Neutropenia (BEN)?

-- Please Select -- ▾

[Cancel](#)

[Next](#)

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0.2 Patient Lab Intake 1

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[Start](#) [Intake](#) [Lab Info](#) [Finish](#)

Lab Information

The Treatment Status and Monitoring Frequency for the patient have been defaulted based on program rules. If you need to change the values you may do so in the fields provided below. Additionally, if you have lab information you may enter it now; otherwise, please press **Next** to continue.

Mike Jones

Lab Entry

ANC value (per μ L)

Blood Draw Date

[Verify Lab](#)

Treatment Status

Pretreatment ▾

Monitoring Frequency

Weekly ▾

Lab	Current	Highest	Lowest
Blood Draw Date	None	None	None
ANC value (per μ L) ?	None	None	None

[Cancel](#) [Next](#)

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1.3 Patient Lab Intake with Treatment Rationale 0

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[Start](#) [Intake](#) [Lab Info](#) [Finish](#)

Lab Information

The Treatment Status and Monitoring Frequency for the patient have been defaulted based on program rules. If you need to change the values you may do so in the fields provided below. Additionally, if you have lab information you may enter it now; otherwise, please press **Next** to continue.

Mike Jones

Lab Entry

ANC value (per μ L)

Blood Draw Date

[Modify Lab](#)

Lab	Current	Highest	Lowest
Blood Draw Date	None	None	None
ANC value (per μ L)	None	None	None

Treatment Status

Treatment Rationale

Treatment Rationale Duration

Monitoring Frequency

I attest that this patient is terminally ill/in hospice care and monitoring can be reduced per the label.

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0.4 ANC Calculator

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ANC Calculator

WBC count (x10 ⁹ /mm ³)	Segs (%)	Bands (%)	ANC value (per μ L)
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

WBC count (x10 ⁹ /mm ³)	Neutrophils (%)	ANC value (per μ L)
<input type="text"/>	<input type="text"/>	<input type="text"/>

[Clear](#) [Calculate](#)

NOTE:
For WBC count, data should be entered in decimal format (a value of 4,300 should be entered as 4.3).
For Segs, Bands, or Neutrophils, data should be entered without percent sign (20% should be entered as 20).
If the ANC value is populated with a value, the same value is populated in the ANC value field on the form.

Source: Mosby's Diagnostic and Laboratory Test Reference, 8th ed. 2003. White blood cell count and differential, page 942.

Lab Information

The Treatment Status and Monitoring Frequency are required to be entered in the fields provided below.

Frank Adam

Lab Entry

ANC value (per μ L)

Blood Draw Date

[Modify Lab](#)

Treatment Status

Treatment Rationale

Treatment Rationale Duration

Monitoring Frequency

I attest that this patient is terminally ill/in hospice care and monitoring can be reduced per the label.

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. Stakeholder Profiles

Stakeholder profiles are accessed via the drop down next to the signed in user's name at the top of every page. **1**

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11 1 Prescriber Profile .

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My Profile

My Information [Edit](#)

First Name / MI

Last Name

Credentials ▾

Clinic / Practice Name

Address

Address 2

City

State / Zip Code ▾

Phone / Ext

Fax

Contact Preference ▾

DEA

NPI

My Certification

Certification ID: **HCP123456789**

Education Program

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.2 Prescriber Designee Profile 1

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My Profile

My Information Edit

First Name

Last Name

Phone / Ext

Fax

Contact Preference

My Certification

Certification ID: [HCP123456789](#)

Education Program

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11 3 Authorized Representative Profile .

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My Profile

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First Name


Last Name


Credentials


Phone / Ext

Fax

Contact Preference

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11 4 Chain Authorized Representative Profile

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My Profile

My Information Edit

First Name


Last Name

Position / Title

Phone / Ext

Fax

Contact Preference

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11.5 Chain Headquarters Profile

The chain authorized representative will have two options via the drop down next to the signed in users name at the top of every page; one for My Profile (authorized representative profile above) and Chain Headquarters Profile (below).



My Profile

My Information Edit

First Name:

Last Name:

Position/Title:

Phone / Ext:

Fax:

Contact Preference:

Chain Name:

Address:

Address 2:

City:

State / Zip:

Phone / Ext:

Fax:

Chain ID:

My Certification

Certification ID: **FAC258523458**

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.6 Pharmacy Staff Profile 1

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My Profile

My Information Edit

First Name

Last Name

Phone / Ext

Fax ▾

Contact Preference

My Enrollment

Enrollment ID: **HCP123456789**

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2. My Account

Account pages are accessed via the drop down next to the signed in user's name at the top of every page.

2. Change Username



Change Username

To change your username, please provide your new username below. The information you provide for your username must be unique within the Clozapine REMS Program website.

Use Email Address as Username [Suggest Username](#)
[Change Password](#)
[Change Email Address](#)

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1 . Change Username Confirmation 2

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Change Username

✔ Your username has been successfully saved.

To change your username, please provide your new username below. The information you provide for your username must be unique within the Clozapine REMS Program website.

Use Email Address as Username [Suggest Username](#)
[Change Password](#)
[Change Email Address](#)

[Cancel](#) [Save](#)

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2.3 Change Password 1

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Change Password

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[Change Email Address](#)

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2.4 Change Password Confirmation 1

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Change Password

✔ Your password has been successfully saved.

To change your password, please complete the fields below.

[Change Username](#)
[Change Email Address](#)

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1 .5 Change Email Address 2

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Change Email Address

To change your email address, please complete the fields below.

[Change Username](#)
[Change Password](#)

[Cancel](#) [Save](#)

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2.6 Change Email Address Confirmation 1

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Change Email Address

✔ Your email address has been successfully updated. A verification email has been sent to <email address>. Please use the link within the email to confirm this change.

To change your email address, please complete the fields below.

[Change Username](#)
[Change Password](#)

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13. Patient Groups

13.1 Manage Groups

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Manage Groups

The table below contains all of your patient groups. If you need to add a new patient group, please use the **Add Group** button.

[Add Group](#)

Group Name	Actions
Group A	-- Please Select -- <input type="button" value="Go"/>
Group B	-- Please Select -- <input type="button" value="Go"/>

[My Dashboard](#)

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The manage groups page will include a list of all groups the prescriber or designee has created for themselves. The actions the prescriber and designee can take are:

- 1 – Add Group – will take the user to the Add Group page
- 2 – Change Group Name – will take the user to the Edit Group page
- 2 – Remove Group – will take the user to the Remove Group page

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3.2 Add Group 1

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Add Group

To add a new group, please specify the group name below and press **Submit**. You can add a patient to the group by accessing the patients profile.

[Cancel](#) [Submit](#)

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3.3 Change Group Name 1

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Change Group Name

To change the group, simply edit the group name in the field below and press **Submit**.

Group Name

[Cancel](#) [Submit](#)

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3.4 Remove Group 1

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Remove Group

To remove the group below simply press **Remove**; otherwise, press **Cancel** to return to Manage Groups.

Group Name: **Group A**

[Cancel](#) [Remove](#)

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13.5 Remove Group Warning 8

The screenshot displays the Clozapine REMS website interface. At the top, the logo 'CLOZAPINE REMS' is visible, along with the tagline 'The Single Shared System for Clozapine' and 'No Blood, No Drug™'. The user 'Summer Hogan' is logged in, and a 'My Dashboard' button is present. A navigation menu includes 'Home', 'Prescriber', 'Pharmacy', 'Patient', 'Resources', 'Important Safety Information', and 'Support'. The main content area shows a 'Remove Group' section with a text input field containing 'Group A'. A warning dialog box is overlaid on the page, featuring a red warning icon and the text: 'Warning', 'Patients are currently assigned to the group you are removing.', and 'Would you like to reassign all the patients to a new group?'. The dialog box has 'No' and 'Yes' buttons. Below the dialog box, there are 'Cancel' and 'Remove' buttons. At the bottom of the page, there is a footer with the text: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' and a navigation bar with links for 'Privacy', 'Terms of Use', 'Site Map', 'FAQs', and 'Contact Us'.

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3.6 Reassign Patients 1

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Reassign Patients

Please select the new group below and press **Submit**.



Group Name:

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14. Dashboard 8

14.1 Dashboard Alerts and Notifications

14.1.1 Dashboard Alerts

Alerts will be displayed for all stakeholders. The Alerts and Notifications tabs are common across all stakeholders.

The screenshot shows the 'Alerts' tab selected in the dashboard. The header includes the Clozapine REMS logo and navigation links. Below the tabs, a message states: 'All program alerts are listed below. Please use the link within an alert to take the necessary action to satisfy the alert.' A search bar is present. A table displays one alert entry:

Alert Date	Alert Category	Alert Reference Name	Alert Subject
03/02/2015	Certification	Hogan, Summer	Begin Certification

Showing 1 of 1 entries

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14.1.2 Dashboard Notifications

Notifications will be displayed for all stakeholders. The Alerts and Notifications tabs are common across all stakeholders.

The screenshot shows the Clozapine REMS dashboard interface. At the top, the user is identified as Summer Hogan, with a 'My Dashboard' button. The main navigation bar includes links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. Below this, there are tabs for Alerts (1), Notifications (1), Patients, and Designees. The Notifications tab is active, displaying a message: 'All program notifications are listed below. Please select a notification and use the Acknowledge button to clear the notification.' A search bar is present. A table lists one notification:

<input type="checkbox"/>	Notification Date	Notification Category	Notification Reference Name	Notification Subject
<input type="checkbox"/>	01/15/2015	General	Hogan, Summer	Certification Confirmation

Below the table, it says 'Showing 1 of 1 entries' and has pagination controls for 1 to 10. An 'Acknowledge' button is located at the bottom right of the notification area.

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4.2 Prescriber Dashboard

14.2.1 Prescriber Dashboard Patient Tab Collapsed 1

Summer Hogan ▾ My Dashboard

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Alerts ¹ Notifications ¹ Patients Designees Manage Groups

The table below contains the patients you have treated with clozapine. If you do not find a patient, please use the Enroll Patient button to add the patient. A flagged row indicates an NNRMF patient.

[Enroll Patient](#) [Eligibility Check](#)

First Name	Last Name	DOB	Treatment Status	Enrollment Status	Group	Relationship	Actions
Anantharaman	Manickavasagam	11/15/1980	Interrupted	Enrolled	Group A	Active	-- Please Select -- <input type="button" value="Go"/>
Chester	Smith	03/05/1983	Active	Enrolled	Group B	Active	-- Please Select -- <input type="button" value="Go"/>
Jane	Brown	07/13/1975	Pretreatment	Incomplete	Group C	Transferred	-- Please Select -- <input type="button" value="Go"/>
Mike	Jones	11/07/1977	Active	Incomplete	Group D	Active	-- Please Select -- <input type="button" value="Go"/>
Terry	White	01/15/1988	Active	Enrolled	Group E	Active	-- Please Select -- <input type="button" value="Go"/>

Showing 10 of 10 entries 1 > 10 ▾

= NNRMF (National Non-Rechallenge Master File) Patients

For definitions of terms used on this page, click [here](#).

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14.2.2 Prescriber Dashboard Patient Tab Expanded

Summer Hogan ▾ My Dashboard

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Alerts ¹ Notifications ¹ Patients Designees Manage Groups

Enroll Patient Eligibility Check Search

The table below contains the patients you have treated with clozapine. If you do not find a patient, please use the Enroll Patient button to add the patient. A flagged row indicates an NNRMF patient.

First Name	Last Name	DOB	Treatment Status	Enrollment Status	Group	Relationship	Actions
Anantharaman	Manickavasagam	11/15/1980	Interrupted	Enrolled	Group A	Active	-- Please Select -- Go
Chester	Smith	03/05/1983	Active	Enrolled	Group B	Active	-- Please Select -- Go
Enrollment ID: PAT123456 Gender: Male NNRMF: No BEN: No		View ANC Monitoring table			Current	Highest	Lowest
		Blood Draw Date	N/A	N/A	N/A		
		ANC value (per µL)	N/A	N/A	N/A		
Jane	Brown	07/13/1975	Pretreatment	Incomplete	Group C	Transferred	-- Please Select -- Go
Mike	Jones	11/07/1977	Active	Incomplete	Group D	Active	-- Please Select -- Go
Terry	White	01/15/1988	Active	Enrolled	Group E	Active	-- Please Select -- Go

Showing 10 of 10 entries 1 10 ▾

= NNRMF (National Non-Rechallenge Master File) Patients

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h dashboard for th pr scrib r will includ a list of all pati nts th pr scrib r is managing.
h actions th pr scrib r can tak ar :

For pati nts with an nrollment status of "Incomplete" th pr scrib r can "Resume Pati nt Enrollment"

1 – nroll Pati nt – will tak th us rs to th Pati nt Intak pag and through th pati nt nrollment proc ss

2 – ligibility Ch ck – will tak th us rs to th ligibility Ch ck pag . *This page will not be available until the 12/14 launch.*

For pati nts with an nrollment status of "Enrolled" th pr scrib r can tak th following actions:

3 – Add Lab – will tak th us r to th Lab Information pag

3 – Chang r atment Status – will tak th us r to th Lab Information pag

3 – Chang r atment ational – will tak th us r to th Lab Information pag

3 – Vi w Pati nt History – will tak th us r to th Pati nt History pag

3 – Vi w Pati nt Profil – will tak th us r to th Pati nt Profil pag

4 – For d finitions of t rms us d on this pag – will pop-up th d finitions on th pag (s n xt mockup) T

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4.2.3 Definitions of Terms Pop-up 1

Definition of Terms

Treatment Status

Pretreatment - Patient has been enrolled in the Clozapine REMS Program, prior to beginning therapy on clozapine

Active - Patient is actively taking clozapine

Interrupted - Patient is temporarily removed from clozapine therapy

Discontinued - Patient is removed from clozapine therapy (includes permanent discontinuation due to severe neutropenia or other reasons, patient death, etc...)

Enrollment Status

Enrolled (for patients and pharmacy staff) - All enrollment requirements have been met

Certified (for all other stakeholders) - All certification requirements have been met

Incomplete - Requirements for enrollment or certification have not been met and must be continued

BEN Patient - Benign Ethic Neutropenia (BEN) is a condition observed in certain ethnic groups whose average ANC's are lower than "standard" laboratory ranges for neutrophils. Because of this condition, patients who have been diagnosed with BEN have a separate ANC monitoring algorithm when treated with clozapine

NNRMF - Patients were listed in the National Non-Rechallenge Master File (NNRMF) if a patient had a WBC less than 2,000/ μ L or an ANC less than 1000/ μ L. All patients who were listed in the NNRMF, and all their lab data were transferred into the Clozapine REMS Program

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4.2.4 Add Lab, Change Treatment Status, Change Monitoring Frequency, and Change Treatment Rationale for Prescribers

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Lab Information

The Treatment Status and Monitoring Frequency for the patient have been defaulted based on program rules. If you need to change the values you may do so in the fields provided below. Additionally, if you have lab information you may enter it now; otherwise, please press **Next** to continue.

Mike Jones

Lab Entry

ANC value (per μL)

Blood Draw Date

[Modify Lab](#)

Lab	Current	Highest	Lowest
Blood Draw Date	None	None	None
ANC value (per μL)	None	None	None

Treatment Status

Treatment Rationale

Treatment Rationale Duration

Monitoring Frequency

I attest that this patient is terminally ill/in hospice care and monitoring can be reduced per the label.

[Cancel](#) [Next](#)

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14.2.5 View Patient History Lab History Tab 8

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Patient History

Lab History Treatment Status History Monitoring Frequency History

Name **Chester Smith**
DOB **03/5/1983**
Gender **Male**

Entry Date	Blood Draw Date	ANC
01/27/2015	01/26/2015	1570
02/27/2015	02/26/2015	900
03/27/2015	03/26/2015	1650

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4.2.6 View Patient History Treatment Status Tab 1

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Patient History

	Lab History	Treatment Status History	Monitoring Frequency History	
Name Chester Smith				
DOB 03/5/1983				
Gender Male				
	Entry Date	Treatment Status	Rationale	Duration
	01/27/2015	Active		
	02/27/2015	Interrupted		
	02/27/2015	Active	Benefit Outweighs Risk	07/27/2015

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4.2.7 View Patient History Monitoring Frequency Tab 1

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Patient History

Lab History Treatment Status History **Monitoring Frequency History**

Name Chester Smith	Entry Date ▾	Monitoring Frequency ▾
DOB 03/5/1983	01/27/2015	Monthly
Gender Male		

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14.2.8 View Patient Profile 8

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Patient Profile

Patient Information

[Edit](#)

First Name

Last Name

DOB

Zip Code

Gender

Race

Group

BEN Patient

NNRMF Patient

Patient Enrollment Information

Enrollment ID: [PAT132456789](#)

[Cancel](#) [Save](#)

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14.2.9 Eligibility Check 8

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Eligibility Check

This Eligibility Check is only intended for **inpatient pharmacy** use to determine if the safe use conditions have been met for your inpatient to receive clozapine. Please complete the Eligibility Check information below and **Submit**. If you have lab updated information you wish to also submit for your inpatient, you may enter it here. The results of the Eligibility Check will be displayed after the information is submitted. All fields below are required unless otherwise indicated.

Patient Information

?

▾

▾

At least **one** identifier is required

[Cancel](#) [Submit](#)

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Pr scribe Eligibility Check Screen (1.2.9) and Pr scribe Design Eligibility Check Screen (1.3.7):

- The eligibility check will be the only option for selection from web dashboards for prescribers, prescriber designees, pharmacist authors, and pharmacist staff (for both inpatient and outpatient pharmacists) for Phase 2 (Oct 12th through Dec 14th) to allow any stakeholder to check eligibility before PDA functionality is available.
- The eligibility check fields have been updated to not require manufacturer and NDC knowing that some manufacturers that prescribers or their designees may have or know.
- At PDA launch (Dec 14th), prescribers, prescriber designees, authorized representatives and pharmacist staff for **inpatient** pharmacists will only have the option to access patient eligibility check from their dashboard (not PDA)
 - Additional Point: For consistency, functionality has been provided to both Prescribers and Prescriber Designees.
- At PDA launch (Dec 14th), authorized representatives and pharmacist staff for **outpatient** pharmacists will only have the option to access patient PDA request from their dashboard (not eligibility).
- Instructions on the Pr scribe and Pr scribe Design Eligibility Check Screens have been updated to clearly explain the purpose of the eligibility check.

14.2.10 Prescriber Dashboard Designees Tab

The table below contains all the designees that are currently assigned or requesting approval from you. If you need to add a new designee to your list, please use the **Add Designee** button.

First Name	Last Name	Certification ID	Approval Status	Actions
Anantharaman	Manickavasagam	HCP123456	Approved	-- Please Select -- Remove Designee
Chester	Smith	HCP123456	Approved	-- Please Select --
Jane	Brown	HCP055254	Pending	-- Please Select -- Approve Designee
Mike	Jones	HCP173277	Approved	-- Please Select --
Terry	White	HCP173285	Approved	-- Please Select --

Showing 10 of 10 entries

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The dashboard for the prescriber will include a list of all designees the prescriber is associated to. The actions the prescriber can take are:

- 1 – Add Designee – will take the user to the Add Designee page
- 2 – Remove Designee – will take the user to the Remove Designee page
- 3 – Approve Designee – will take the user to the Approve Designee page

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1 .2.11 Add Designee with Results 4

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Add Designee

To add a designee, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Designee Information

<input type="text" value="Terry"/>	<input type="text" value="White"/>	<input type="text" value="Certification ID (opt)"/>
<input type="text" value="Phone (opt)"/>	<input type="text" value="Fax (opt)"/>	<input type="text" value="Email (opt)"/>

[Search](#)

If the search results have returned the designee you want to associate to, please select the row and press **Submit**. If you do not see the designee you are looking for, please try your search again or contact the designee to ensure they are certified in the program.

First Name	Last Name	Phone
Terry	White	555-555-5555

Showing 1 of 1 entries

[Cancel](#) [Submit](#)

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1 .2.12 Remove Designee 4

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Remove Designee

Removing this designee will revoke their ability to perform actions on your behalf. To continue, please check the box below and press **Submit**.

Designee Name: **Anantharaman Manickavasagam**

Certification ID: **HCP123456**

I hereby remove this designee's ability to perform actions on my behalf in the Clozapine REMS Program.

Cancel

Submit

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1 .2.13 Approve Designee 4

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Designee Determination

This designee will act on my behalf in fulfilling the requirements for the Clozapine REMS Program.

Designee Name: **Jane Brown**

Certification ID: **HCP055254**

Decline

Approve

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4.3 Prescriber Designee Dashboard

14.3.1 Prescriber Designee Dashboard Patient Tab 1 Collapsed

The table below contains the patients you have treated with clozapine. If you do not find a patient, please use the Enroll Patient button to add the patient. A flagged row indicates an NNRMF patient.

First Name	Last Name	DOB	Treatment Status	Enrollment Status	Group	Relationship	Actions
Anantharaman	Manickavasagam	11/15/1980	Interrupted	Enrolled	Group A	Active	-- Please Select -- Go
Chester	Smith	03/05/1983	Active	Enrolled	Group B	Active	-- Please Select -- Go
Jane	Brown	07/13/1975	Pretreatment	Incomplete	Group C	Transferred	-- Please Select -- Go
Mike	Jones	11/07/1977	Active	Incomplete	Group D	Active	-- Please Select -- Go
Terry	White	01/15/1988	Active	Enrolled	Group E	Active	-- Please Select -- Go

Showing 10 of 10 entries

= NNRMF (National Non-Rechallenge Master File) Patients

For definitions of terms used on this page, click [here](#).

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14.3.2 Prescriber Designee Dashboard Patient Tab Expanded

The table below contains the patients you have treated with clozapine. If you do not find a patient, please use the Enroll Patient button to add the patient. A flagged row indicates an NNRMF patient.

First Name	Last Name	DOB	Treatment Status	Enrollment Status	Group	Relationship	Actions
Anantharaman	Manickavasagam	11/15/1980	Interrupted	Enrolled	Group A	Active	-- Please Select -- Go
Chester	Smith	03/05/1983	Active	Enrolled	Group B	Active	-- Please Select -- Go
Jane	Brown	07/13/1975	Pretreatment	Incomplete	Group C	Transferred	-- Please Select -- Go
Mike	Jones	11/07/1977	Active	Incomplete	Group D	Active	-- Please Select -- Go
Terry	White	01/15/1988	Active	Enrolled	Group E	Active	-- Please Select -- Go

Showing 10 of 10 entries

Legend: NNRMF (National Non-Rechallenge Master File) Patients

For definitions of terms used on this page, click [here](#).

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The dashboard for the prescriber designee will include a list of all patients the designee's prescribers are managing. The actions the prescriber designee can take are:

For patients with an enrollment status of "Incomplete" the prescriber designee can "Resume Patient Enrollment"

1 – Enroll Patient – will take the users to the Patient Intake page and through the patient enrollment process

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2 – Eligibility Check – will take the users to the Eligibility Check page. *This page will not be available until the 12/14 launch.*

For patients with an enrollment status of “Enrolled” the prescriber can take the following actions:

3 – Add Lab – will take the user to the Lab Information page

3 – Change Treatment Status – will take the user to the Lab Information page

3 – View Patient History – will take the user to the Patient History page

3 – View Patient Profile – will take the user to the Patient Profile page

4 – Definitions of terms used on this page – will pop-up the definitions on the page (see next mockup) y

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4.3. Definitions of Terms Pop-up 1

Definition of Terms

Treatment Status

Pretreatment - Patient has been enrolled in the Clozapine REMS Program, prior to beginning therapy on clozapine

Active - Patient is actively taking clozapine

Interrupted - Patient is temporarily removed from clozapine therapy

Discontinued - Patient is removed from clozapine therapy (includes permanent discontinuation due to severe neutropenia or other reasons, patient death, etc...)

Enrollment Status

Enrolled (for patients and pharmacy staff) - All enrollment requirements have been met

Certified (for all other stakeholders) - All certification requirements have been met

Incomplete - Requirements for enrollment or certification have not been met and must be continued

BEN Patient - Benign Ethic Neutropenia (BEN) is a condition observed in certain ethnic groups whose average ANC's are lower than "standard" laboratory ranges for neutrophils. Because of this condition, patients who have been diagnosed with BEN have a separate ANC monitoring algorithm when treated with clozapine

NNRMF - Patients were listed in the National Non-Rechallenge Master File (NNRMF) if a patient had a WBC less than 2,000/ μ L or an ANC less than 1000/ μ L. All patients who were listed in the NNRMF, and all their lab data were transferred into the Clozapine REMS Program

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4.3.2 Add Lab and Change Treatment Status for Prescriber 1 Designees

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Lab Information

The Treatment Status and Monitoring Frequency for the patient have been defaulted based on program rules. If you need to change the values you may do so in the fields provided below.

Mike Jones

Lab Entry

ANC value (per μ L)

Blood Draw Date

Treatment Status

Active ▾

Treatment Rationale

-- Please Select -- ▾

Monitoring Frequency

-- Please Select -- ▾

Alert this prescriber that this patient should be under hospice care.

Lab	Current	Highest	Lowest
Blood Draw Date	None	None	None
ANC value (per μ L) ?	None	None	None

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1 .3.3 View Patient History Lab History Tab 4

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Patient History

Lab History Treatment Status History Monitoring Frequency History

Name **Chester Smith**
DOB **03/5/1983**
Gender **Male**

Entry Date	Blood Draw Date	ANC
01/27/2015	01/26/2015	1570
02/27/2015	02/26/2015	900
03/27/2015	03/26/2015	1650

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4.3.4 View Patient History Treatment Status Tab 1

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Patient History

Lab History **Treatment Status History** Monitoring Frequency History

Name **Chester Smith**
DOB **03/5/1983**
Gender **Male**

Entry Date	Treatment Status	Rationale	Duration
01/27/2015	Active		
02/27/2015	Interrupted		
02/27/2015	Active	Benefit Outweighs Risk	07/27/2015

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4.3.5 View Patient History Monitoring Frequency Tab 1

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Patient History

	Lab History	Treatment Status History	Monitoring Frequency History
Name Chester Smith	Entry Date		Monitoring Frequency
DOB 03/5/1983	01/27/2015		Monthly
Gender Male			

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4.3.6 View Patient Profile 1

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[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Patient Profile

Patient Information

[Edit](#)

First Name

Last Name

DOB

Zip Code

Gender ▾

Race ▾

Group ▾

BEN Patient No

NNRMF Patient No

Patient Enrollment Information

Enrollment ID: [PAT132456789](#)

[Cancel](#) [Save](#)

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4.3.7 Eligibility Check 1

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Summer Hogan ▾ [My Dashboard](#)

[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Eligibility Check

This Eligibility Check is only intended for **inpatient pharmacy** use to determine if the safe use conditions have been met for your inpatient to receive clozapine. Please complete the Eligibility Check information below and **Submit**. If you have lab updated information you wish to also submit for your inpatient, you may enter it here. The results of the Eligibility Check will be displayed after the information is submitted. All fields below are required unless otherwise indicated.

Patient Information

?

▾

▾

At least **one** identifier is required

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14.3.8 Prescriber Designee Dashboard Prescribers Tab

Summer Hogan ▾ My Dashboard

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Alerts ¹ Notifications ¹ Patients Prescribers

The table below contains all the prescribers you are currently a designee for. If you need to be a designee for a prescriber not in your list, please use the **Associate to Prescriber** button.

Associate to Prescriber Search

Last Name	First Name	Certification ID	Approval Status	Actions
Anantharaman	Manickavasagam	HCP123456	Approved	-- Please Select --
Chester	Smith	HCP223245	Approval Pending	Remove Designee Relationship -- Please Select --
Jane	Brown	HCP173277	Approved	Cancel Designee Request -- Please Select --
Mike	Jones	HCP373240	Approved	-- Please Select -- Go
Terry	White	HCP173285	Approved	-- Please Select -- Go

Showing 10 of 10 entries

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The dashboard for the prescriber designee will include a list of all prescribers the designee is acting on behalf of. The actions the prescriber designee can take are:

- 1 – Associate to Prescriber – will take the user to the Associate to Prescriber page
- 2 – Remove Designee Relationship – will take the user to the Remove Designee Relationship page
- 3 – Cancel Designee Request – will take the user to the Cancel Designee Request page

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14.3.9 Associate to Prescriber 8



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[Forgot Username?](#) [Forgot Password?](#) [Need an Account?](#)

[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Associate to Prescriber

To associate to a prescriber, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Prescriber Information (at least one identifier is required):

<input type="text" value="Terry"/>	<input type="text" value="White"/>	and	<input type="text" value="TW1234567"/>	or	<input type="text" value="NPI"/>
<input type="text" value="Phone (opt)"/>					

If the search results have returned the prescriber you want to associate to, please select the row and press **Submit**. If you do not see the prescriber you are looking for, please try your search again or contact the prescriber to ensure they are certified in the program.

First Name	Last Name	Phone	DEA	NPI
Terry	White	555-555-5555	TW1234567	

Showing 1 of 1 entries

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4.3. 0 Remove Designee Relationship 1

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Remove Designee Relationship

To remove your relationship with this prescriber, please check the box below and press **Submit**.

Prescriber Name: **Summer Hogan**

Relationship Status: **Approved**

I hereby remove my relationship with this prescriber and understand that I will no longer have the ability to perform actions on their behalf in the Clozapine REMS Program.

[Cancel](#) [Submit](#)

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4.3. Cancel Designee Request 1

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Cancel Designee Request

To cancel the approval request to act on behalf of this prescriber, please check the box below and press **Submit**.

Prescriber Name: **Summer Hogan**

Relationship Status: **Pending**

I hereby cancel my request to act on behalf of this prescriber in the Clozapine REMS Program.

Cancel

Submit

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14.4 Pharmacy Dashboard

14.4.1 Pharmacy Dashboard Pharmacies Tab

Summer Hogan ▾ My Dashboard

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Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Alerts ³ Notifications ¹ **Pharmacies** Pharmacy Staff

Please search for your pharmacy in the table below and take the appropriate action. If you need to add a new pharmacy to your list, please use the Add Pharmacy button. For patient actions, use the Actions list below.

Add Pharmacy Search

Pharmacy Name	Address	Pharmacy Type	Certification ID	Certification Status	Actions
Joey's Apothecary	1 East Main Street, New York NY 10001	Inpatient	FAC1002345831	Certified	-- Please Select -- Go
Hogan RX	2 Park Avenue, New York NY 10201	Independent Outpatient	FAC2234583304	Certified	Add Lab and Eligibility Check View Pharmacy Profile Remove Pharmacy Go
Walgreens	311 Bell Road, Anaheim CA 92805	Inpatient	FAC0057124807	Incomplete	-- Please Select -- Go
CVS	423 Main Street, Tampa FL 33614	Inpatient	FAC0057124807	Incomplete	-- Please Select -- Go
Rite Aid	52 Milky Way Dr, Anchorage, AK 99508	Inpatient	FAC2585234583	Certified	Resume Pharmacy Certification -- Please Select -- Go

Showing 10 of 10 entries

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The dashboard for the authorized representative of inpatient and outpatient pharmacy types will include a list of all pharmacies the authorized representative is managing. The actions the authorized representative can take are:

1 – Add Pharmacy – will take the users to the Pharmacy Intake page and through the pharmacy certification process

For pharmacies with an enrollment status of “Certified” the authorized representative can take the following actions:

2 – Add Lab and Eligibility Check – will take the user to the Add Lab and Eligibility Check page. *This page will only be available between 10/12 and 12/14. On 12/14, PDA will take over and Eligibility Check will be removed.*

2 – Add Lab and Predisense Authorization – will take the user to the Add Lab and Predisense Authorization page. *This page will not be available between 10/12 and 12/14. On 12/14, PDA will take over and Eligibility Check will be removed.*

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- 2 View Pharmacy Profile will take the user to the Pharmacy Profile page
- 2 Move Pharmacy will take the user to the Move Pharmacy page
- 3 For pharmacists with an enrollment status of "Incomplete" the authorized representative can "Resume Pharmacy Certification"

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14.4.2 Add Lab and Eligibility Check 8

Summer Hogan ▾ [My Dashboard](#)

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[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Eligibility Check

To determine if the safe use conditions have been met for your patient to receive clozapine, please complete the Eligibility Check information below and **Submit**. If you have lab information for your patient you may enter it here. The results of the Eligibility Check will be displayed after the information is submitted. All fields listed below are required unless otherwise indicated.

Patient Information

Add Patient Lab (optional)

Eligibility Check Request (optional)

[?](#)

At least one identifier is required

[Cancel](#) [Submit](#)

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4.4.3 Eligibility Check Result – Unsuccessful

This result is displayed for both the Predispose Authorization and the Eligibility Check when the result is unsuccessful.

The screenshot shows the Clozapine REMS website interface. At the top, the logo and tagline are present. A navigation menu includes links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. A user profile for Summer Hogan and a My Dashboard link are visible in the top right. The main heading is "Eligibility Check Result". A prominent red warning box states: "Do not dispense clozapine to this patient." Below this, a patient profile for Chester Smith is shown with fields for Name and DOB. To the right, a list of reasons for the failed check is provided: the patient is not enrolled, the prescriber is not certified, and the lab status is "Lab was not saved". A note advises contacting the prescriber for further assistance. A footer contains contact information and a call to action: "For additional information about the Clozapine REMS Program, please call 844-267-8678." A bottom navigation bar includes links for Privacy, Terms of Use, Site Map, FAQs, and Contact Us.

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4.4.4 Add Lab and Predispose Authorization 1

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[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Predispose Authorization

To determine if the safe use conditions have been met for your patient to receive clozapine, please complete the Predispose Authorization information below and **Submit**. If you have lab information for your patient you may enter it here. The results of the Predispose Authorization will be displayed after the information is submitted. All fields listed below are required unless otherwise indicated.

Patient Information

Add Patient Lab (optional)

Predispose Authorization Request

?

At least one identifier is required

[Cancel](#) [Submit](#)

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4.4.5 Predispense Authorization Result – Successful

This result is displayed for both the Predispense Authorization and the Eligibility Check when the result is successful.

The screenshot displays the Clozapine REMS web interface. At the top, the logo and tagline 'The Single Shared System for Clozapine No Blood, No Drug™' are visible. A user profile for 'Summer Hogan' and a 'My Dashboard' button are in the top right. A navigation menu includes 'Home', 'Prescriber', 'Pharmacy', 'Patient', 'Resources', 'Important Safety Information', and 'Support'. The main heading is 'Predispense Authorization'. A green-bordered box contains a checkmark and the text: 'You are now authorized to dispense clozapine to the below patient.' Below this, a table lists patient details: Name: Chester Smith, DOB: 03/05/1983, and Predispense Authorization Code: XXXXXXX. To the right, 'Lab Status' is 'Lab was saved'. A footer note states: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' The bottom navigation bar includes 'Privacy', 'Terms of Use', 'Site Map', 'FAQs', and 'Contact Us'.

Name	Chester Smith	Lab Status	Lab was saved
DOB	03/05/1983		
Predispense Authorization Code	XXXXXXXX		

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14.4.6 View Pharmacy Profile 8

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Summer Hogan ▾ [My Dashboard](#)

[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Pharmacy Profile

Pharmacy Information Edit

Pharmacy Name

Pharmacy Type

Address

Address 2

City

State / Zip Code

Phone / Ext

Fax

NCPDP

DEA

NPI

Pharmacy Certification Information

Certification ID: **HCP123456789**

[Cancel](#) [Save](#)

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14.4.7 Remove Pharmacy 8

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Summer Hogan ▾ My Dashboard

Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Remove Pharmacy

Removing this pharmacy will deactivate it from the Clozapine REMS Program. The pharmacy will no longer be authorized to dispense clozapine. To continue, please check the box below and press **Submit**.

Pharmacy Name: **Joey's Apothecary**

Certification ID: **PRS123456789**

I hereby remove this pharmacy from the Clozapine REMS Program.

Cancel

Submit

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14.4.8 Pharmacy Dashboard Pharmacy Staff Tab

The screenshot shows the 'Pharmacy Staff' tab selected in a dashboard. The dashboard header includes the user name 'Summer Hogan' and a 'My Dashboard' button. The main navigation bar contains links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. Below the navigation, there are tabs for Alerts, Notifications, Pharmacies, and Pharmacy Staff. A search bar is located above the table. The table lists one pharmacy staff member: Sally Smith, associated with Joey's Apothecary, located at 1 East Main Street, New York NY 10001, with enrollment ID HCP123456789 and status Enrolled. An 'Actions' dropdown menu is open for the first row, showing options: '-- Please Select --' and 'Remove Pharmacy Staff'. A callout box with the number '1' points to the 'Remove Pharmacy Staff' option. The page indicates 'Showing 1 of 1 entries'.

First Name	Last Name	Pharmacy Name	Address	Enrollment ID	Enrollment Status	Actions
Sally	Smith	Joey's Apothecary	1 East Main Street, New York NY 10001	HCP123456789	Enrolled	-- Please Select -- Remove Pharmacy Staff

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The dashboard for the authorized representative of inpatient and outpatient pharmacy types will include a list of all pharmacy staff that is representing the authorized representative. The actions the authorized representative can take are:

- 1 – Remove Pharmacy Staff – will take the user to the Remove Pharmacy Staff page

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14.4.9 Remove Pharmacy Staff 8

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Summer Hogan ▾ My Dashboard

Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Remove Pharmacy Staff

Removing this pharmacy staff member will revoke their ability to perform actions on behalf of this pharmacy. To continue, please check the box below and press **Submit**.

Staff Member: **Sally Smith**

Pharmacy Name: **Joey's Apothecary**

Enrollment ID: **HCP123456789**

I hereby remove this pharmacy staff member's ability to perform actions on behalf of this pharmacy in the Clozapine REMS Program.

[Cancel](#) [Submit](#)

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14.5 Chain Pharmacy Dashboard

14.5.1 Chain Pharmacy Dashboard Pharmacies Tab

The screenshot displays the 'Pharmacies' tab of the Chain Pharmacy Dashboard. At the top, there is a navigation bar with the CLOZAPINE REMS logo and the tagline 'The Single Shared System for Clozapine No Blood, No Drug™'. The user is identified as 'Summer Hogan' and is on the 'My Dashboard' page. The main content area features a navigation menu with 'Alerts', 'Notifications', 'Pharmacies', and 'Pharmacy Staff'. Below this, there is a section for adding and managing stores, including an 'Add Chain Store' button and a search bar. A table lists the following pharmacies:

Store Name	Address	Certification ID	Certification Status	Actions
Joey's Apothecary	1 East Main Street, New York NY 10001	FAC1002345831	Certified	-- Please Select -- Go
Hogan RX	2 Park Avenue, New York NY 10201	FAC2234583304	Certified	View Pharmacy Profile Remove Pharmacy
Apollo Pharmacy	311 Bell Road, Anaheim CA 92805	FAC0057124807	Incomplete	-- Please Select -- Go
Life Pharmacy	423 Main Street, Tampa FL 33614	FAC0057124807	Certified	-- Please Select -- Go
Mercury Drug	52 Milky Way Dr, Anchorage, AK 99508	FAC2585234583	Certified	-- Please Select -- Go

At the bottom of the table, it indicates 'Showing 10 of 10 entries' and a 'Certify Store' button.

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The dashboard for the authorized representative of chain pharmacy headquarters will include a list of all chain store pharmacies the authorized representative is managing. The actions the authorized representative can take are:

1 – Add Chain Store – will take the users to the Chain Pharmacy Store Intake page and through the chain store certification process

For pharmacies with an enrollment status of "Certified" the authorized representative can take the following actions:

2 – View Pharmacy Profile – will take the user to the Pharmacy Profile page

2 – Remove Pharmacy – will take the user to the Remove Pharmacy page

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– For pharmacists with a certification status of “Incomplete” the authorized representative can check on , numerous, or all checkboxes (located on the left side of the data grid) and press the Certify Storage button to certify the storage once the staff is trained.

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14.5.2 View Pharmacy Profile 8

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Summer Hogan ▾ [My Dashboard](#)

[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Pharmacy Profile

Pharmacy Information Edit

Pharmacy Name

Pharmacy Type

Address

Address 2

City

State / Zip Code

Phone / Ext

Fax

NCPDP

DEA

NPI

Pharmacy Certification Information

Certification ID: [HCP123456789](#) 🖨️

[Cancel](#) [Save](#)

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1 .5.3 Remove Pharmacy 4

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Summer Hogan ▾ My Dashboard

Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Remove Pharmacy

Removing this pharmacy will deactivate it from the Clozapine REMS Program. The pharmacy will no longer be authorized to dispense clozapine. To continue, please check the box below and press **Submit**.

Pharmacy Name: **Joey's Apothecary**

Certification ID: **PRS123456789**

I hereby remove this pharmacy from the Clozapine REMS Program.

Cancel

Submit

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14.5.4 Chain Pharmacy Dashboard Pharmacy Staff Tab

The screenshot shows the 'Pharmacy Staff' tab selected in a dashboard. The dashboard header includes the user's name 'Summer Hogan' and a 'My Dashboard' button. The main navigation bar contains links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. Below the navigation bar, there are tabs for Alerts, Notifications, Pharmacies, and Pharmacy Staff. The Pharmacy Staff tab is active, displaying a table of staff members. A search bar is located at the top right of the table area. The table has columns for First Name, Last Name, Pharmacy Name, Address, Enrollment ID, Enrollment Status, and Actions. One staff member, Sally Smith, is listed with details for her pharmacy, address, and enrollment ID. The Actions column for Sally Smith shows a dropdown menu with the option 'Remove Pharmacy Staff' selected. A callout box with the number '1' points to this option. Below the table, it indicates 'Showing 10 of 10 entries'.

The table below contains all the pharmacy staff that are currently assigned to you.

First Name	Last Name	Pharmacy Name	Address	Enrollment ID	Enrollment Status	Actions
Sally	Smith	Joey's Apothecary	1 East Main Street, New York NY 10001	HCP123456789	Enrolled	-- Please Select -- Remove Pharmacy Staff

Showing 10 of 10 entries

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The dashboard for the authorized representative of chain pharmacy headquarters will include a list of all pharmacy staff that is representing the authorized representative. The actions the authorized representative can take are:

1 – Remove Pharmacy Staff – will take the user to the Remove Pharmacy Staff page

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1 .5.5 Remove Pharmacy Staff 4

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Summer Hogan ▾ My Dashboard

Home Prescriber Pharmacy Patient Resources Important Safety Information Support

Remove Pharmacy Staff

Removing this pharmacy staff member will revoke their ability to perform actions on behalf of this pharmacy. To continue, please check the box below and press **Submit**.

Staff Member: **Sally Smith**

Pharmacy Name: **Joey's Apothecary**

Enrollment ID: **HCP123456789**

I hereby remove this pharmacy staff member's ability to perform actions on behalf of this pharmacy in the Clozapine REMS Program.

[Cancel](#) [Submit](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

14.6 Pharmacy Staff Dashboard

14.6.1 Pharmacy Staff Dashboard Pharmacies Tab

The screenshot shows the CLOZAPINE REMS Pharmacy Staff Dashboard. The top navigation bar includes 'New Staff' and 'My Dashboard'. The main navigation menu includes 'Home', 'Prescriber', 'Pharmacy', 'Patient', 'Resources', 'Important Safety Information', and 'Support'. The 'Pharmacies' tab is selected, and a callout box labeled '1' points to the 'Associate to Pharmacy' button. Below the button is a search bar. The main content area contains a table of pharmacies with columns for Pharmacy Name, Address, Certification Status, and Actions. A callout box labeled '2' points to the 'Add Lab and Eligibility Check' option in the Actions column. The table lists seven pharmacies: Berry Store, Cherry Store, Complete Pharmacy Name, Complete Training STORE, New Apple Store, Pharmacy One, and Test Pharmacy. The bottom of the dashboard includes a footer with 'Privacy | Terms of Use | Site Map | FAQs | Contact Us' and a message: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.'

Pharmacy Name	Address	Certification Status	Actions
Berry Store	Address One, TAMPA, Florida 33004	Certified	-- Please Select -- Go
Cherry Store	Address Two, ORLANDO, Florida 32807	Certified	Add Lab and Eligibility Check Go
Complete Pharmacy Name	Address, WEST MONROE, Louisiana 71291	Certified	-- Please Select -- Go
Complete Training STORE	Address, MIAMI, Florida 33135	Certified	-- Please Select -- Go
New Apple Store	Address, MALIBU, California 90265	Certified	-- Please Select -- Go
Pharmacy One	Address, SHREVEPORT, Louisiana 71109	Certified	-- Please Select -- Go
Test Pharmacy	1234123434, MONROE, Louisiana 71201	Certified	-- Please Select -- Go

The dashboard for the pharmacy staff will include a list of all pharmacies the pharmacy staff is representing. The actions the pharmacy staff member can take are:

1 – Associate to Pharmacy – will take the user to the Associate to Pharmacy page

2 – Add Lab and Eligibility Check – will take the user to the Add Lab and Eligibility Check page. *This page will only be available between 10/12 and 12/14. On 12/14, PDA will take over and Eligibility Check will be removed.*

2 – Add Lab and Predisense Authorization – will take the user to the Add Lab and Predisense Authorization page. *This page will not be available between 10/12 and 12/14. On 12/14, PDA will take over and Eligibility Check will be removed.*

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4.6.2 Associate to Pharmacy 1

CLOZAPINE REMS
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Summer Hogan ▾ [My Dashboard](#)

[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Associate to Pharmacy

To identify the pharmacy you represent, please complete the fields below and press **Search**. All fields listed below are required unless otherwise indicated.

Pharmacy Information (at least one identifier is required):

<input type="text" value="10001"/>	and	<input type="text" value="DEA"/>	<input type="text" value="NPI"/>	<input type="text" value="3456789"/>
------------------------------------	-----	----------------------------------	----------------------------------	--------------------------------------

If the search results have returned your record, please highlight the row and press **Submit**. If you do not see your record, please try your search again or contact the Clozapine REMS Program for assistance.

Pharmacy Name	Pharmacy Address	Pharmacy Phone
CVS	423 Main Street, Tampa FL 33614	555-555-5555

Showing 1 of 1 entries

For additional information about the Clozapine REMS Program, please call 844-267-8678.

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1 .6.3 Add Lab and Eligibility Check 4

Summer Hogan ▾ [My Dashboard](#)

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[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Eligibility Check

To determine if the safe use conditions have been met for your patient to receive clozapine, please complete the Eligibility Check information below and **Submit**. If you have lab information for your patient you may enter it here. The results of the Eligibility Check will be displayed after the information is submitted. All fields listed below are required unless otherwise indicated.

Patient Information

Add Patient Lab (optional)

Eligibility Check Request (optional)

?

▾

▾

At least one identifier is required

For additional information about the Clozapine REMS Program, please call 844-267-8678.

[Privacy](#) | [Terms of Use](#) | [Site Map](#) | [FAQs](#) | [Contact Us](#)

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4.6.4 Eligibility Check Result – Unsuccessful

This result is displayed for both the Predispose Authorization and the Eligibility Check when the result is unsuccessful.

The screenshot shows the Clozapine REMS website interface. At the top, the logo and tagline are present. A navigation menu includes links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. A user profile for Summer Hogan and a My Dashboard link are also visible. The main heading is "Eligibility Check Result". A prominent warning box states: "Do not dispense clozapine to this patient." Below this, a patient profile for Chester Smith is shown with fields for Name and DOB. To the right, a list of reasons for the failed eligibility check is provided:

- ✘ The patient is not enrolled in the REMS program
- ✘ The prescriber is not certified in the REMS program
- ✘ Acceptable patient lab is not on file
- ✘ **Lab Status Lab was not saved**

Below the list, a note reads: "For further assistance with this patient's eligibility, please contact the patient's prescriber." A printer icon is located at the bottom right of the patient information section. At the bottom of the page, a footer contains the text: "For additional information about the Clozapine REMS Program, please call 844-267-8678." and a navigation bar with links for Privacy, Terms of Use, Site Map, FAQs, and Contact Us.

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4.6.5 Add Lab and Predispose Authorization 1

CLOZAPINE REMS
The Single Shared System for Clozapine
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Summer Hogan ▾ [My Dashboard](#)

[Home](#) [Prescriber](#) [Pharmacy](#) [Patient](#) [Resources](#) [Important Safety Information](#) [Support](#)

Predispose Authorization

To determine if the safe use conditions have been met for your patient to receive clozapine, please complete the Predispose Authorization information below and **Submit**. If you have lab information for your patient you may enter it here. The results of the Predispose Authorization will be displayed after the information is submitted. All fields listed below are required unless otherwise indicated.

Patient Information

Add Patient Lab (optional)

Predispose Authorization Request

?

At least one identifier is required

[Cancel](#) [Submit](#)

For additional information about the Clozapine REMS Program, please call 844-267-8678.

[Privacy](#) | [Terms of Use](#) | [Site Map](#) | [FAQs](#) | [Contact Us](#)

CLOZAPINE REMS

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1 .6.6 Predispose Authorization Result – Successful

This result is displayed for both the Predispose Authorization and the Eligibility Check when the result is successful.

The screenshot displays the Clozapine REMS web interface. At the top, the logo and tagline 'The Single Shared System for Clozapine No Blood, No Drug™' are visible. A navigation bar includes links for Home, Prescriber, Pharmacy, Patient, Resources, Important Safety Information, and Support. A user profile for 'Summer Hogan' and a 'My Dashboard' button are in the top right. The main heading is 'Predispose Authorization'. A green-bordered box contains a checkmark and the text: 'You are now authorized to dispense clozapine to the below patient.' Below this, a table lists patient information: Name: Chester Smith, DOB: 03/05/1983, and Predispose Authorization Code: XXXXXXX. To the right, 'Lab Status' is shown as 'Lab was saved'. At the bottom, a footer contains the text: 'For additional information about the Clozapine REMS Program, please call 844-267-8678.' and a navigation bar with links for Privacy, Terms of Use, Site Map, FAQs, and Contact Us.

Name	Chester Smith	Lab Status	Lab was saved
DOB	03/05/1983		
Predispose Authorization Code	XXXXXXX		

This is a r r s a i f a l c r i c r c r d h a w a s s i g d
l c r i c a l l y a d h i s a g i s h m a i f s a i f h l c r i c E
s i g a u r .

/s/ E

MITCH LL V Mathis E
09/15/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019758Orig1s061

OTHER REVIEW(S)

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan E. Blair, Health Communications Analyst, DRISK

From: Lisa Hubbard, Deputy Division Director, DAPR1, OPDP

CC: Mathilda Fienkeng, Team Leader, OPDP
Louis Flowers, RPM, OSE
Kim Lehrfeld, Team Leader, DRISK
Cathy Miller, Risk Management Analyst, DRISK
Kate Heinrich Oswell, Health Communications Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: June 19, 2015

Re: **NDA 019758** CLOZARIL (clozapine) tablets, for oral use
NDA 021590 FAZACLO (clozapine) orally disintegrating tablets
NDA 203479 VERSACLOZ (clozapine) oral suspension
ANDA 074949 clozapine tablets
ANDA 076809 clozapine tablets
ANDA 075417 clozapine tablets
ANDA 075713 clozapine tablets
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials for the Clozapine Single Shared System

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for the Clozapine Single Shared System.

- HCP and Patient REMS Materials:
 - Clozapine REMS Important Safety Information

The version of the draft REMS materials used in this review were provided by DRISK (Joan Blair) via email on June 1, 2015. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for the Clozapine Single Shared System.

General Comment

Please remind the CPMG that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program:

- HCP and Patient REMS Materials
 - Clozapine REMS Important Safety Information (ISI)

Specific Comments

- Clozapine REMS Important Safety Information
 - The following statements appear inconsistent with the recommendations in section 5.1 and 2.4 of the draft CPMG Clozapine PI,

-  (b) (4)

Specifically, section 5.1 of the draft CPMG Clozapine PI refers to section 2.4 for recommended ANC monitoring which states:

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 $\geq 1500/\mu\text{L}$ and for BEN patients until their ANC is $\geq 1000/\mu\text{L}$ or above their baseline.

We have no additional comments on the proposed REMS materials at this time.

Thank you for your consult.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSANNAH O'DONNELL
06/19/2015

LISA M HUBBARD
06/19/2015

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan E. Blair, Health Communications Analyst, DRISK

From: Susannah O'Donnell, Regulatory Review Officer, OPDP

CC: Mathilda Fienkeng, Team Leader, OPDP
Louis Flowers, RPM, OSE
Kim Lehrfeld, Team Leader, DRISK
Cathy Miller, Risk Management Analyst, DRISK
Kate Heinrich Oswell, Health Communications Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: January 14, 2015

Re: **NDA 019758** CLOZARIL (clozapine) tablets, for oral use
NDA 021590 FAZACLO (clozapine) orally disintegrating tablets
NDA 203479 VERSACLOZ (clozapine) oral suspension
ANDA 074949 clozapine tablets
ANDA 076809 clozapine tablets
ANDA 075417 clozapine tablets
ANDA 075713 clozapine tablets

Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials for the Clozapine Single Shared System

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for the Clozapine Single Shared System.

- Healthcare Provider (HCP) REMS Materials:
 - Chain Pharmacy Enrollment Form
 - Pharmacy Enrollment Form
 - (b) (4)
 - Prescriber Enrollment Form
 - Prescriber Designee Enrollment Form
 - Patient Enrollment Form
 - Distributor Enrollment Form
 - HCP Guide
 - HCP Overview Guide
 - HCP Knowledge Assessment
 - ANC Reporting Form
- Direct-to-Consumer (Patient) REMS Materials:
 - Guide for Patients and Caregivers
- HCP and Patient REMS Materials:
 - Clozapine Products Manufacturers Group (CPMG) Website Screen Captures

The version of the draft REMS materials used in this review were provided by DRISK (Joan Blair) via email on December 29, 2014. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for the Clozapine Single Shared System.


General Comment


Please remind the CPMG that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program:

- Healthcare Provider (HCP) REMS Materials:
 - Chain Pharmacy Enrollment Form
 - Pharmacy Enrollment Form
 - (b) (4)
 - Prescriber Enrollment Form
 - Prescriber Designee Enrollment Form
 - Distributor Enrollment Form

- OPDP is concerned that while the underlined claim may be accurate, within the context of the REMS, it is promotional in tone and minimizes the risk of severe neutropenia by implying that patients should be rechallenged with clozapine regardless of this risk. We recommend deleting the underlined claim.
- Page nine of the HCP Guide includes a section titled, (b) (4)
 (b) (4)

- OPDP is concerned that this presentation minimizes the risks associated with clozapine (b) (4)
 (b) (4)

- **Guide for Patients and Caregivers**

- Page one of the Guide for Patients and Caregivers includes a section which states:

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

 (b) (4)

- OPDP is concerned that this list does not include all of the possible symptoms of neutropenia of which patients should be aware. OPDP recommends revising this list of symptoms to include all of the following symptoms of neutropenia

[agranulocytosis], as stated in “**What is the most important information I should know about VERSACLOZ?**” (b) (4)

[...] Tell your healthcare provider right away if you have any of the following symptoms of agranulocytosis:

- 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
- **Clozapine Products Manufacturers Group (CPMG) Website Screen Captures**
 - OPDP reminds the CPMG to update the titles of the downloadable Program Materials on the website as necessary. For example, (b) (4) should be updated to the current title, “What You Need to Know About Clozapine and Neutropenia: a Guide to Patients and Caregivers.”
 - OPDP is unable to comment on the content of the FAQs on page 23 of the Website Screen Captures, as it was not included for our review.

We have no further comments on these proposed REMS materials at this time.

Thank you for your consult.

60 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSANNAH O'DONNELL
01/14/2015

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019758Orig1s061

**RISK ASSESSMENT AND RISK MITIGATION
REVIEW(S)**

Department of Health and Human Services
Federal Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date: September 14, 2015

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., MPH.
Health Communications Analyst, DRISK

Kate Oswell, M.A.
Health Communications Analyst, DRISK

Team Leader: Kim Lehrfeld, Pharm.D., DRISK

Acting Deputy Division Director: Rekha Mehta, Pharm.D., M.P.H., DRISK

Acting Division Director: Cynthia LaCivita, Pharm.D., DRISK

Drug Name(s): Clozapine

Therapeutic class: Atypical antipsychotic

OND Review Division: Division of Psychiatry Products

Subject: Review of Single Shared System REMS

OSE RCM#: 2013-2345

Drug	Application Number	Sponsor	Date Received	eCTD Sequence #/ Supporting doc
Clozaril	NDA 019758	HLS Therapeutics	9/14/2015	0073/472
Clozapine	ANDA 202873	Accord	9/14/2015	0016/017
Clozapine	ANDA 074949 ANDA 076809 ANDA 203039 ANDA 90308	Teva	9/14/2015 9/14/2015 9/14/2015 9/14/2015	0014/347 0013/191 0014/016 0008/37
	ANDA 075417 ANDA 201824	Mylan	9/14/2015 9/14/2015	0040/138 0026/030
	ANDA 075713	Caraco/Sun	9/14/2015	0017/128
	ANDA 203807	Actavis (now Allergan)	9/14/2015	0020/021
Fazaclo ODT	NDA 021590	Jazz	9/14/2015	0023/349
Versacloz	NDA 203479	Jazz	9/14/2015	0070/104

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7 2A 2 ACHME 2 S/APPE 2DED 2FO 2MA 2 O 2 ... 2 36 2

2

d

EXECUTIVE SUMMARY

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the single shared system (SSS) risk evaluation and mitigation strategy (REMS) for clozapine and recommend approval of the proposed REMS submitted by the Clozapine Product Manufacturers Group (CPMG) on September 14, 2015.

Clozapine is an antipsychotic approved in 1989. It is available in the US as an oral tablet (Clozaril and generics), orally disintegrating tablet (Fazaclon and authorized generic), and an oral suspension (Versacloz). Because of the risk of severe neutropenia, at the time of initial US approval, Clozaril was approved with a restricted distribution program. As clozapine ANDAs and new formulations were approved, each manufacturer developed a separate but comparable restricted distribution program for their product(s). Clozapine was included on the list of products deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of FDA Amendments Act (FDAAA). As part of the "determine REMS" review process, FDA determine a SSSR was necessary to encompass all clozapine products due to the burden of having several separate but comparable programs. In addition, the Division of Psychiatry Products (DPP) re-evaluated clozapine labeling with regard to how best to address the risk of severe neutropenia and determined the neutropenia monitoring recommendations and treatment algorithms were outdated and required revision.

The proposed REMS submitted September 14, 2015 incorporates all clozapine products under a shared program to provide a centralized point of communication for prescribers and pharmacists and supports the updated labeling.

The REMS is comprised of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRISK recommends approval of the REMS appended to this review.

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the single shared system (SSS) risk evaluation and mitigation strategy (REMS, or SSSR) for clozapine-containing products. The Clozapine SSSR applies to the Sponsors and products included in the table on pages 1 and 2 of this review, which form the Clozapine Product Manufacturer's Group (CPMG). The CPMG initially submitted a proposed REMS on September 18, 2014, via email (and formally to their respective applications on September 25, 26, and 29, 2014), and last amended their proposed REMS submission on September 14, 2015 for individual NDA and ANDA applications (see table on pages 1 and 2 of this review).

The proposed Clozapine SSSR, (i.e., Clozapine REMS Program) consists of elements to assure safe use (ETASU; prescriber certification, pharmacy certification, documentation of safe use conditions, patient monitoring, and a patient enrollment in a registry), an implementation system, and a timetable for submission of assessments.

1.1 PRODUCT BACKGROUND

Clozapine is an antipsychotic approved in the United States (US) in 1989. It is available in the US as an oral tablet (Clozaril and generics), orally disintegrating tablet (Fazaclon and authorized generic), and an oral suspension (Versacloz).

Clozapine is a category 1 controlled substance (Schedule I) under the Controlled Substances Act (21 U.S.C. 812). Clozapine is a Schedule I controlled substance because it has a high potential for abuse, it has no currently accepted medical uses in the United States, and it has a high potential for abuse. Clozapine is a Schedule I controlled substance because it has a high potential for abuse, it has no currently accepted medical uses in the United States, and it has a high potential for abuse. Clozapine is a Schedule I controlled substance because it has a high potential for abuse, it has no currently accepted medical uses in the United States, and it has a high potential for abuse.

Because of the risk of agranulocytosis, at the time of its initial approval, Clozaril was approved under a Risk Evaluation and Mitigation Strategy (REMS) program. Prior to 2007, a clozapine ANDA was not allowed. On March 27, 2008, the Food and Drug Administration (FDA) took effect provisions of the Food and Drug Administration Amendments Act (FDAAA) that authorized the requirement of a REMS for certain drugs. Clozapine was the first drug to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of FDAAA.² The purpose of such a product with a REMS program is to ensure the safety and effectiveness of the drug. On September 16, 2008, the FDA approved a new formulation of clozapine with a REMS because the original formulation was not safe. The FDA approved the new formulation of clozapine with a REMS because the original formulation was not safe.

As part of the “deemed REMS” review process, FDA determined that a REMS was necessary to compare all clozapine products to the burden of having a comparable program. On July 30-31, 2012, REMS Notification Letters were sent to the sponsors of all ANDAs and NDAs that hold a patent “[a]ny drug that involves all potential holders of approved applications for a clozapine product to the burden of the health care system and the safety of the clozapine. It would improve the community of clozapine holders, help to ensure appropriate patient care and a quality of life for a user of clozapine therapy. Furthermore, it would improve compliance by training the prescribers and the pharmacist in the burden of the health care system that the REMS program for the clozapine products.”

In addition, FDA became aware of the strategy/program practice that was derived from the comments on the approval label. The Division of Psychiatry Products (DPP) re-evaluated clozapine label with regard to how best to address the risk of uterine cancer in the uterine cancer patients. The comments on the approval label for the clozapine were as follows:

¹ Clozaril [package insert]. East Hanover, NJ:Novartis Pharmaceutical Corporation;2014.

² See Federal Register Notice “Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategy (REMS) for Purpose of the Food and Drug Administration Amendments Act of 2007” (73 FR 16313, March 27, 2008).

³ Vancloz was approved on February 6, 2013 with a REMS. It is the only clozapine product with an approved REMS.

⁴ For format of the label for vanclozine, refer to the revised compliance by Duca, LE. See the DARRTS on August 15, 2014 by Duca LE.

- Neutrophils below the minimum threshold (ANC) by B
- The ANC thresholds for the clinical effectiveness relative to B
- Patients with the highest neutrophil count (EN) have severe neutropenia more often B
- Patients who experience a decrease in severe neutropenia by the clinical effectiveness B
 are being compared with the effectiveness of the rescriber determined by the effectiveness of B
 clinical effectiveness relative to the weight of the risk of severe neutropenia. This B
 choice of the minimum threshold for the NBBINB-RechBgeMasterFile B
 (NNRMF).⁵ B

B
 The SSSR will be going to have a different label. B

1.2 DISEASE BACKGROUND B

Schizophrenia is a severely disabling mental illness, characterized by a loss of touch with reality, extreme social withdrawal, and abnormal behavior. This is a severe mental illness that is often treated with medication. They require frequent medical supervision (including hospitalization) and often require a combination of medication and therapy. The disease is often fatal, with a 10% mortality rate. B

Schizophrenia affects approximately 1% of the U.S. population. But only 10% of these patients are able to meet the definition of a first responder. At least 10% of these patients are able to meet the definition of a first responder. At least 10% of these patients are able to meet the definition of a first responder. At least 10% of these patients are able to meet the definition of a first responder. At least 10% of these patients are able to meet the definition of a first responder. B

Clozapine is a second-generation antipsychotic. Other FDA-approved second-generation antipsychotics include risperidone, olanzapine, and quetiapine. Of these products, Zyrtec (levamisole) is the only product currently approved with REMS. The goal of the Zyrtec REMS is to mitigate the risk of agranulocytosis by ensuring that patients are monitored closely. The goal of the Zyrtec REMS is to mitigate the risk of agranulocytosis by ensuring that patients are monitored closely. The goal of the Zyrtec REMS is to mitigate the risk of agranulocytosis by ensuring that patients are monitored closely. B

1.3 REGULATORY HISTORY B

The following summarizes the regulatory history relevant to the development of the Clozapine SSS B
 REMS: B

B

⁵ NNRMF is a national database to identify patients who meet clozapine's current "no rechallenge" criteria (WBC less than 2,000/ μ L or ANC less than 1000/ μ L). Only patients who meet these standard criteria are eligible for the registry. All patients are required to be re-evaluated by the NNRMF to determine if they are eligible for B- B
 rechallenge. B

⁶ Source: IMS Health, TTP Patient Tracker (TPT), Y2014, Extracted AUG2015. B

⁷ See JC, et al. First-Generation Antipsychotics for Children and Young Adults. *Current Psychiatry Reports*. Rev. 2013. (Prepared by the University of Alberta, Evidence-based Practice Center under Contract N290-2007-10021.) B
 AHRQ Publication N290-2007-10021-EF. Rockville, MD. Agency for Healthcare Research and Quality. February 2012. B

- Sept 2018 Sponsors of cizapine-containing products submitted proposed REMS per March 27, 2018 Federal Register notice.
- July 2019 Division of Pharmacovigilance (DPV) I review identified 14 patients with agranulocytosis who received cizapine despite meeting non-recall engagement criteria.
- Sept 2019 REMS Notification Letter *drafted* to inform all sponsors to develop a SSSR. Letter included a document outlining the REMS to assist Sponsors with development of a SSSR.
- April 2018 Draft REMS Notification Letter with attached SSSR Document sent through internal clearance. The REMS Notification Letters were not sent until 2/12 due to issues that were raised during clearance.

FDA-drafted SSSR Document required prescribers to report patients deemed non-recall eligible but prescribed cizapine. This requirement deviated from the recommendations in the labeling and required further discussion before the REMS Notification Letters and FDA-drafted REMS Document could be finalized.
- April - June 2018 CDER discussed the patient registry practices that deviate from approved labeling.
- June 2018 DPP proposed modification to the agranulocytosis section of labeling to address the following concerns:
 - How patients to be recalled in certain situations.
 - Recognize a distinct patient population with BEN who previously may not qualify for treatment with cizapine.
- Aug 2018 The Division of Hematology Products (DHP) completed a consult to review proposed labeling changes in light of the current understanding of neutropenia, particularly in patients with BEN. DHP recommended removing white blood cell count as a monitoring parameter for neutropenia, lowering the ANC thresholds for treatment interruption, patients with BEN may be considered for cizapine treatment.
- Oct 2018 DPP obtained Novartis' Cizari® label approved in the United Kingdom (UK) and the Cizari patient monitoring service (CPMS) recommendations, a monitoring service in the UK that supervises the prescribing of cizapine and the hematologic testing.
- June 2018 External Special Government Employee (SGE) consult request was initiated and delayed six months due to clearance issues.
- Jan 2012 DPP began to update the neutropenia monitoring recommendations in the Warnings and Precautions section of the label, including the addition of a

separate unit r u al ur th uf r pat e ts w th BEN u

- Feb 2012: u SGE c p leted the c us lt a d rec e ded f rther s u f ca t cha ues t u the label, cl d u h w t u t r pat e ts w th BEN u
- Feb – May 2012: u DPP c ut ued d sc ss u s f label u, cl d u c rp rat u f the SGE u rec e ded cha ues t the e tr pe u u t r u cr ter a a d the u add t u f separate u t r u cr ter a f r pat e ts w th BEN. u
- Apr 18, 2012: u FDA rece ved a C t ze Pet t u fr u a d v d al phys c a req est u the cl zap u label u be pdated t 1) cl de separate u t r u cr ter a f r u pat e ts w th BEN, a d 2) create a at ual re ustry f treat e t-res sta t u sch z phre u pat e ts w th BEN t all w these pat e ts t be treated w th u cl zap u u
- J u – A u 2012: u A ser es f l ste u sess u s were held v a teleph ue w th uts de expert u psych atr sts, h n at l usts, a d psych atr c phara c sts. The p rp se was u t bta ua better udersta d u f: u
 - C rre t u d cl ual pract ce w th respect t a a u e tr pe u the e eral p p lat u a d pat e ts w th BEN u
 - C rre t cl zap u re ustry perat us a d s u est us f r u p r veu ts u
- J 12 2012: u F ve NDA a d ANDA Sp us rs f re d the Cl zap u REMS Sp us r u Gr up (later re aeu d Cl zap u Pr d ct Ma ufact rers Gr up, CPMG) a d e t t d sc ss ext steps, cl d u uer a ce, le al c utracts a d u a reeu ts t c llab rate t devel p a SSSR. u
- J 130-31, 2012: u FDA f re d the CPMG f the eed t establ sh a SSSR a u “Information Request” Letter (now titled a REMS N u f cat u Letter). u
- Feb 6, 2013: u Versacl z appr ved w th a REMS. Versacl z s incorporated into Jazz’s u Fazacl pat e t re ustry. u
- Feb 2013: u FDA pr v ded pr p sed draft cl zap u label u w th rev sed severe u e tr pe u War u s a d Preca t us sect u t the Sp us rs. u
- Mar 4, 2013: u FDA pr v ded pr p sed rev sed class label u re ard u e tr pe u t all u cl zap u NDA a d ANDA h lders. u
- J u 18, 2013: u FDA held a SSSR devel peu t k ck- ff telec ufere ce w th CPMG. FDA u req ested the CPMG s b ut a REMS pr p sal by A u st 18, 2013. CPMG u stated th s date was very a uress ve. u
- Mar 26 – May 9, 2013: u NDA Sp us rs a d FDA e ut ate class label u f r e tr pe u. u

- Aug 8, R R FDA sent our preliminary recommendations on the SSS R requests for R utilization data from the currently operating registries, and clarified the R FDAs expectation that the CPMG at least submit an outline of the SSS R by August 8, R for our review. R
- Aug R R R CPMG submitted a SSS R outline to FDA. R
- Sep R R R FDA provided comments on the SSS R outline and requested a draft SSS R F document be submitted on or before October 8, R . We also asked for R additional information from the individual member companies about R laboratory submissions to the currently operating registries. R
- Oct 8, R R FDA received a response from the CPMG, which did not include a draft R SSS R document. R
- Dec R R R Joint face-to-face meeting with FDA and CPMG to discuss the CPMG R achievements to date, challenges of implementing a SSS R and action plan R for addressing the challenges. R
- Sep 8, R4 R CPMG submitted a proposed SSS R for review. R
- Oct 5, R4 R FDA received a Citizen Petition from a health system to modify the R clozapine EMS to accommodate patients with BEN. R
- Oct R R4 R FDA met with the CPMG to discuss concerns with the proposed SSS R In R particular, CPMG’s initial SSS R proposal did not support safe use of R clozapine given the proposed labeling changes and did not provide for a R centralized communication infrastructure to facilitate the necessary R information exchange. R
- Dec R R4 R CPMG submitted an amended proposed SSS R for review (R und). This R amendment included a proposal to implement a predispose authorization R requirement for outpatient dispensing. R
- Feb R R5 R During a teleconference CPMG informed FDA that development of the R SSSR is on hold until certain “high impact” issues are resolved. These high impact items were: use of the phrase “treatment rationale,” capturing who R reports ANCs (b)(4), inpatient pharmacy reporting R requirements, transition plan feedback, Patient Enrollment Form revisions, R use of a single Pharmacy Enrollment Form regardless of pharmacy type, R prescriber designed R role, and program terminology consistency, R
- Mar R R R5 R FDA and CPMG held a face-to-face meetings to resolve the “high impact” R issues. R

- Mar 17 01 (ISK presented to the EMS Oversight Committee (OC)⁸ and obtained concurrence to delineate the prescriber designee role in the SSS ((
- Apr 17 01 (CPMG submitted an amended proposed SSS (for review (ound 3). This (amendment reflected agreement on issues addressed during the March 11- (1 (01 face-to-face. In particular F (A conveyed the decision on the (prescriber designee role (ISK identified the program design was not (aligned with labeling with regard to BEN designation and that labeling (needed to address hospice patients. (
- May 8 01 (CPMG submitted the Clozapine EMS website screenshots. F (A identified CPMG proposal to implement an abbreviated version of the *Guide for* (*Healthcare Providers* was problematic because the education should be (consistent regardless of the format healthcare providers use to receive (education. (
- Jun 6 01 (CPMG submitted an amended proposed SSS (for review (ound 4). (ISK provided substantial editing and comments to improve the clarity (and construction of the materials but did not identify fundamental problems with the program. (
- Jul 10 01 (CPMG submitted Clozapine EMS website screenshots. (
- Aug 14 01 (CPMG submitted an amended proposed SSS (for review (ound). (
- Aug 8 01 (CPMG submitted amended Clozapine EMS website screenshots. (
- Sep14 01 (CPMG submitted amended proposed SSS (Final). (

2 MATERIALS REVIEWED (

2.1 SUBMISSIONS (

- The following reviews were completed for the initial proposed SSS (submitted on September 18 (014 (ound 1) (
 - Robottom S. (ISK review signed into A (TS on November 19 014 by obottom S (and Lehrfeld K. (
 - Robottom S. (ISK review signed into A (TS on December 3 014 by obottom S and (Lehrfeld K. (
 - Robottom S. (ISK review signed into A (TS on December 19 014 by obottom S and (Lehrfeld K. (

⁸ As per the 1st Century review process all EMS with elements to assure safe use (ETASU) are discussed at the EMS (Oversight Committee (OC) which consists of senior level management from the Offices of New Drugs Surveillance and (Epidemiology and Regulatory Policy. (

- 4
- The fo o 4 rev e 4 as comp eted for the proposed SSSR subm ited o December 23, 201 . 4
(Rou d 2) 4
 - Robottom S. DRISK rev e 4s 4 ed DARRTS o Ju e 19, 2015 by Robottom S a d 4
Lehrfe d K. 4
- 4
- The fo o 4 rev e 4 as comp eted for the proposed SSSR subm ited o Apr 17, 2015 (Rou d 3) 4
 - Robottom S. DRISK rev e 4s 4 ed DARRTS o Au ust 5, 2015 by Robottom S a d 4
Lehrfe d K. 4
- 4
- The fo o 4 rev e 4 as comp eted for the proposed SSSR subm ited Ju e 26, 2015 (Rou d) 4
 - Robottom S. DRISK rev e 4s 4 ed DARRTS o Au ust , 2015 by Robottom S a d 4
Lehrfe d K. 4
- 4
- The fo o 4 rev e 4 as comp eted for the proposed SSSR subm ited Au ust 1 , 2015 (Rou d 5) 4
 - Robottom S. DRISK rev e 4s 4 ed DARRTS o September 11, 2015 by Robottom S a d 4
Lehrfe d K. 4
- 4
- CPMG Proposed C ozap 4 SSSR subm ited September 8 a d 10, 2015 v a ema a d to d v dua 4
NDA a d ANDA app cat o s o September 11-1 , 2015. 4

2.2 OTHER MATERIALS INFORMING OUR REVIEW 4

- 4
- REMS Not f cat o Letters. S 4 ed DARRTS o Ju y 30-31, 2012. 4
- Du ca LE. Labe 4 rev e 4S 4 ed DARRTS o Au ust 15, 201 by Du ca LE. 4

3 CPMG's PROPOSED SSSR FOR CLOZAPINE-CONTAINING PRODUCTS 4

I the Ju y 30-31, 2012 REMS Not f cat o Letters formed the spo sors that, at m i num, the SSSR 4
be requ red to cude: 4

- Med cat o Gu de 4
- ETASU descr bed as fo o 4: 4
 - A requ reme t that hea thcare prov ders ho prescr be C ozar (c ozap 4) are 4
spec a y cert f ed. To become cert f ed, presc rbers sha attest to hav 4 comp eted 4
the tra 4 a d sha e ro the c ozap 4 REMS pro ram. 4
 - A requ reme t that c ozap 4 o 4y be d spe sed by pharmac es (c ud 4 4
pharmac es hosp ta s a d other hea thcare sett 4s) that are spec a y cert f ed. To 4
become cert f ed, pharmac es sha attest to hav 4 comp eted the tra 4 a d sha 4
e ro the c ozap 4 REMS pro ram. 4
 - A requ reme t that c ozap 4 o 4y be d spe sed to pat e ts 4h docume tat o of 4
safe-use co d t o s. Safe use co d t o s ou d cude ver fy 4 that requ red 4
mo 4tor 4 a d pat e t e 4 b 4ty s co f rmed pr or to the pat e t rece v 4 c ozap 4. 4
 - A requ reme t that each pat e t us 4 c ozap 4 be subject to certa 4mo 4tor 4, 4
c ud 4 obta 4 ANC va ues as spec f ed profess o a abe 4 . 4
 - A requ reme t that each pat e t us 4 c ozap 4 be e ro ed a re 4try. 4

- o Impl me G o Sys G

Th follow Gg summG z s h G l propos d SSSR subm i G by CPMGo S p Gmb r 18, 2014. G

Transition Plan G

[Redacted] (b) (4)

Goal G

[Redacted] (b) (4)

REMS Elements G

- Pr scr b r C r f c G G

[Redacted] (b) (4)

- Ph rm ay C r f c G G

[Redacted] (b) (4)

(b) (4)

- P /ien Moni o ing /

(b) (4)

- P /ien En ollmen /

(b) (4)

- Im plemen / ion Sy /em /

(b) (4)

- Time /ble fo ubmi ion of /e /men / /

(b) (4)

Reviewer Comment: The SSSR CPMG initial proposa

(b) (4)

(b) (4)

DRISK identified several problems with implementing

(b) (4)

(b) (4) These concerns were communicated to CPMG in a teleconference on October 23, 2014. CPMG proposed substantial revisions to the SSSR to address these concerns in the second (December 23, 2014) submission.

In addition, DRISK determined the initial SSSR transition proposal was inadequate. DRISK recommended CPMG propose a multi-faceted transition plan approach leveraging individual-targeted

(letter le re re e t tive i ter ctio F meeti g booth) effort El m F commu ic tio (rofe io Fl F ocietie jour F dverti eme t i ter et) effort to f cilit te the tr F itio from the i dividu l F regitrie to the SSSR to e Eure re criber El h rm Ei t re w Fe of the ew tre tme t El F mo itori g recomme d tio F El the Ed to be certified i the SSSR to co ti ue to re cribe or di E E cloz F e. F

4 FINAL TRANSITION PLAN AND DISCUSSION F

CPMG evaluated several options with regard to how to transition from the six⁹ individual legacy F registries to the new shared system. Based on CPMG analysis, CPMG proposed shutting down the F individual legacy registries concurrent with launching the SSSR. DRISK agreed with CPMG’s proposal. F The advantages of the proposed approach are 1) avoids the need for upgrading the retiring legacy F registries to accommodate the new labeling changes, 2) minimizes confusion for stakeholders with F regard to which system(s) to use, and 3) minimizes data migration challenges with data going into the F individual legacy registries and the SSSR concurrently. However, a limitation of this approach is that it F could not accommodate for a phased launch of the shared system website because CPMG stated it was F too technically complicated to launch only a portion of the Clozapine REMS website F (prescriber/pharmacy certification) separate from the patient management aspect. Therefore, CPMG F proposal did not accommodate for allowing prescribers and pharmacies to certify in advance of needing F to utilize the shared system for patient care. Refer to Section 5.2.1 and Section 5.2.2 for further F discussion. F

The Transition Plan includes four phases as described in the REMS Supporting Document: F

- **Preapproval:** This phase includes multiple iterations of data migration from the legacy registries F to the SSSR. All available prescriber and pharmacy data along with all available patient data F from the last three years is migrated into the SSSR. All available data in the NNRMF will be F migrated into the SSSR. F
- **Phase 1 (Day 0 through Day 29):** For the first thirty days post-SSSR approval, the legacy F registries will function as usual. The SSSR is not operational. A multi-faceted outreach plan will F launch to alert prescribers and pharmacists about the new labeling changes and SSSR. The F outreach plan includes emails/letters to all registered prescribers and pharmacists in the legacy F registries, a four-page “What’s New with Clozapine: An Overview” will accompany the emails F and letters, letters to professional societies, pop-up notices on legacy registry websites, and pop- F up notices on clozapine product websites. F

Data migration from the legacy registries to the SSSR will occur daily to transfer incoming data F received by the legacy registries that was not previously available for migration. F

- **Phase 2 (Day 30 through Day 90):** Starting on Day 30, the SSSR is operational with the F exception of pre-dispense authorization aspect and the legacy registries are shut down. Legacy F registry websites will automatically direct users to the Clozapine REMS Program F website, and all phone and fax numbers previously associated with individual F clozapine patient registries will be transferred to the Clozapine REMS Program, F

⁹ Jazz Pharmaceuticals maintains one registry with two names, “Fazaclo Patient Registry” and “Versacloz Patient Registry.” F The database is combined into a single registry for both products. F

consolidation of common conditions through the Clozapine REMS Program for clozapine
requirements of prescribers, dispensing, or distribution.

Prescribers: During this time period prescribers must verify in the Clozapine REMS
Program or continue to prescribe clozapine. All prescribers must use the
Clozapine REMS Program web-based system (or phone) to enroll new prescribers
in the current period. Refer to the prescriber certification section for more
information.

Pharmacies: During this time period all pharmacies must verify in the Clozapine
REMS Program or continue to dispense clozapine. Pharmacies must use the
Clozapine REMS Program web-based system (or phone) to verify prescriber
enrollment, and verify the ANC schedule.

Prescribers: New prescribers will be enrolled in the Clozapine REMS Program by
prescribers; existing prescribers will be re-enrolled in the Clozapine REMS
Program (no requirement to be re-enrolled).

- **Phase 3 (Day 90) – Full Implementation** occurs including the requirements for
pharmacies to obtain pre-dispensing authorization before dispensing clozapine. A pre-
dispensing authorization must be obtained one of three ways: 1) by enrolling in the
system to support electronic communication with the Clozapine REMS Program, 2) by
submitting a request to the Clozapine REMS Program website, or 3) by calling the
Clozapine REMS call center.

On Day 90, distributors will no longer distribute clozapine products to pharmacies
that do not verify in the Clozapine REMS Program. Pharmacies that do not become
certified will be required to return remaining clozapine stock.

5 FINAL REMS AND DISCUSSION

From September 18, 2014 to present, FDA collaborated with CPMG to develop SSSR. The review
encompasses six rounds of comments (see Section 2.1 for lists of DRISK reviews), weekly
meetings, more than 20 teleconferences with CPMG, and two off-site meetings with CPMG.
The final SSSR is described in the following sections.

5.1 REMS GOALS

The goal of the Clozapine SSSR is to minimize the risk of severe neutropenia associated with the use of
clozapine by:

- Educating prescribers and pharmacies about the risk of severe neutropenia and appropriate
monitoring requirements
- Informing prescribers about the risk of severe neutropenia and appropriate monitoring
requirements
- Ensuring compliance with the monitoring schedule for absolute neutrophil count (ANC) prior to
dispensing clozapine
- Ensuring the prescriber documents risk-benefit assessments when ANC falls below the
schedule and is described in the Prescriber Information

- Esta j s j g o g-term safety a d safe use of c ozap je y e ro j g a pat e ts w jo rece ve j c ozap je t e reg stry j

T e overarc j g goa s to m ĩ gate t e r sk of severe eutrope ja. T e o ect ves sted u der t e goa j support t e spec f c requ reme t t e REMS t at are requ red to e sure safe use. j

5.2 REMS ELEMENTS j

5.2.1 Prescriber Certification j

1. j Hea t care prov ders w jo prescr e c ozap je are spec a y cert f ed. j

a) j To e come spec a y cert f ed to prescr e c ozap je t e C ozap je REMS Program, j ea t care prov ders must: j

- (1) Rev ew t e Prescr j g I format o for c ozap je; j
- (2) Rev ew *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* a d j successfu y comp ete t e *Knowledge Assessment for Healthcare Providers*; a d j
- (3) E ro t e C ozap je REMS Program y comp et g t e *Clozapine REMS Prescriber j Enrollment Form*. j

) j As a co d t o of cert f cat o , prescr ers must: j

(1) E ro eac pat e t t e C ozap je REMS Program y: j

a) j I form i g t e pat e t a out t e r sks assoc ated w t c ozap je c ud jg severe j eutrope ja a d t e C ozap je REMS Program requ reme ts y us g *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*, a d j prov d jg t to t e pat e t or careg ver u jess c j ca udgme t d cates t at t e j patient's adherence to the treatment regimen will be negatively impacted by providing j *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and j Caregivers* j

() Comp et g t e *Clozapine REMS Patient Enrollment Form* for eac pat e t. Su m ĩ j t e comp eted form to t e C ozap je REMS Program a d store a copy t e j patient's records. j

(2) Perform t e fo w j g requ reme ts o a o go jg as s for eac pat e t a d report to t e j C ozap je REMS Program v a t e o j e system, y fax, or y ca j g t e C ozap je REMS j Program co tact ce ter: j

(a) Report ANC accord g to t e mo tor g sc edu e descr ed t e Prescr j g j I format o . j

() Report aut or zat o to co t ue treatme t for pat e ts w t a ANC t at fa s e ow j t e accepta e ra ge descr ed t e Prescr j g I format o , w e t e prescr er j determ i e j t e e ef ts exceed t e r sks of deve op jg severe eutrope ja. j

c) j C ozap je Spo sors must: j

(1) E sure t at ea t care prov ders w o prescr e c ozap je are spec a y cert f ed j accorda ce w t t e requ reme ts descr ed a ove. j

- (2) En R ha h al hca R p ovid R can compl R h c Rifica ion p oc R, pa i n R n ollm en R and manag m en R onlin o by fax o h Clozapin EMS P og am. R
- (3) En R ha h al hca R p ovid R who p Rc ib clozapin a no ifi d wh n h y hav R b R c Rifi d in h Clozapin EMS P og am. R
- (4) Main ain a valida d, c R da aba Rof h al hca R p ovid R who a c Rifi d o R p Rc ib clozapin in h Clozapin EMS P og am. Clozapin Spon o R m u R R ensure that the prescriber's REMS requirements are met and may de-c Rify non- R complian p Rc ib R if h q i m en R do no con in R o b me. RR
- (5) Main ain a valida d, c R da aba Rof pa i n n oll d in h Clozapin EMS R P og am R
- (6) En R ha c Rifi d p Rc ib R a p ovid d acc R o h da aba Rof c Rifi d R pha maci R and n oll d pa i n R R
- (7) P ovid *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* R and *Clozapine and the Risk of Neutropenia: An Overview for Healthcare Providers* o R h al hca R p ovid R who: R
 - (a) R a Rmp o p Rc ib clozapin and a Rno y R c Rifi d, o R
 - (b) R inq i abo R how o b com ec RRifi d. R
- (8) En R ha wi hin 30 cal nda day of EMS app oval, h EMS ma Rial li R R b low a R availabl on h Clozapin EMS P og am w R i R (www.clozapin R m sc R n) o by calling h Clozapin EMS P og am con ac c n R R a 844-267-8678. R

The following ma Rial R po P Rc ib R c Rifica ion: R

- *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* R
- *Knowledge Assessment for Healthcare Providers* R
- *Clozapine REMS Prescriber Enrollment Form* R
- *Clozapine REMS Prescriber Designee Enrollment Form* R

R

Prescriber Certification: Issues identified and addressed during the review cycle R

▪ **Transition process for prescriber certification** R

Giv n h b an ial chang R o h n R op nia moni o ing commen R a ion and la d R clozapin R m en R lgo i hm s a Rong wi h mod R iz d q i m en R ad op R in h Clozapin R EMS P og am compa R o h l gacy gi R , D RSK d R min d i wa n c Ra y fo R p Rc ib R who a gi R d in on o mo of h l gacy gi R o ngag in a c Rifica ion R p oc R fo h Clozapin EMS P og am. P Rc ib R m u R l) vi w h G R d fo H R l hca R R P ovid R, 2) R c Rf lly compl R h H al hca R P ovid Knowl dg A R m en , and 3) R compl R and b mi h P Rc ib R En ollm en R fo m, ag Ring o f lfill h p og am R q i m en R R

CPMG's an i ion plan (d R ib d abov) do Rno allow p Rc ib R and pha maci o c Rify in R advanc of n R ling o iliz h ha R y R m fo pa i n ca R D RSK ai d conc R b ca R i R wo ld l av om ep RRc ib R li l o no im e R c Rify b fo Rn R ling o in Rac wi h h n w R Clozapin EMS y R m; j opa dizing con in i y of clozapin R m en R o pa i n R R

To address this concern, CPMG proposed a “grandfathering” process for all clozapine prescribers who met one of the following:

- Prescribers with patients who have a reported ANC or WBC count in one or more of the legacy registries in the previous 3 years, or
- Prescribers with patients who were listed in the NNRMF

“Grandfathered” prescribers are automatically enrolled (but not certified) in the Clozapine REMS Program providing them access to the Clozapine REMS system to manage their existing patients to minimize treatment interruption. “Grandfathered” prescribers are not able to enroll new patients or identify a patient as diagnosed with BEN until completing the Clozapine REMS certification process. These prescribers must certify in the Clozapine REMS Program within a designated time (up to 6 additional weeks). If the prescriber fails to certify within the designated time frame, the prescriber’s access to the Clozapine REMS Program is suspended until he/she completes certification.

▪ **Completion of knowledge assessment as part of prescriber certification**

Given the substantial changes to the neutropenia monitoring recommendations and related clozapine treatment algorithms along with modernized requirements adopted in the Clozapine REMS Program compared to the legacy registries, DRISK determined it was necessary for prescribers to demonstrate understanding of the labeling changes and program requirements as part of the Clozapine REMS prescriber certification process.

▪ **Utilization of a Prescriber Designee**

A “prescriber designee” is a person(s) who interacts with a REMS system to perform administrative activities on behalf of the certified prescriber. These administrative activities for clozapine may include completing the patient enrollment form, entering ANC results, reporting modification of the treatment status or modification of the monitoring frequency (if the patient is eligible). The purpose of a prescriber designee is to reduce burden on the healthcare system by allowing other individuals to perform administrative tasks for prescribers.

The initial CPMG proposal for prescriber designees (b) (4)
(b) (4)
(b) (4)2) allowed the designee to be a non-healthcare
professiona (b) (4)
(b) (4)

DRISK supported accommodating for the prescriber designee role in the Clozapine REMS Program given the high administrative burden that results from REMS programs that require reporting the results of periodic monitoring to the REMS program. In addition, given the electronic-based nature of this program, the REMS must be constructed to ensure the system is compliant with HIPAA technical safeguards (e.g., unique user name a passwords for all people who interact with the system).

However, DRISK did not suppo (b) (4)
(b) (4)

DRISK presented limiting the prescriber designee role in the SSSR to the REMS Oversight Committee on March 17, 2015. The ROC concurs

5.2.2 Pharmacy Certification

Pharmacies that dispense clozapine are specially certified.

- a) To become specially certified to dispense clozapine in the Clozapine REMS Program, pharmacies must:
 - (1) Designate an authorized representative to complete certification process on behalf of the pharmacy.
 - (a) *Clozapine REMS Pharmacy Enrollment Form*
 - (b) *Clozapine REMS Chain Headquarter Pharmacy Enrollment Form*
 - (2) Ensure the authorized representative will oversee implementation and compliance with the Clozapine REMS Program requirements by doing the following:
 - (a) Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and successfully complete the *Knowledge Assessment for Healthcare Providers*.
 - (b) Ensure all relevant staff involved in the dispensing of clozapine are trained on the Clozapine REMS Program requirements as described in *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and maintain records of staff training.
 - (i) For pharmacies that have a pharmacy management system that supports electronic telecommunication verification, each pharmacist must be trained utilizing established training protocols for their certified pharmacy.
 - (ii) For pharmacies that have a pharmacy management system that does NOT support electronic telecommunication verification, each pharmacist must be trained by reviewing

¹⁰ Meeting Minutes. REMS Oversight Committee March 17, 2015.

Clozapine and the Risk of Neutropenia: A Guide for Health Care Providers on Successfully Completing the Knowl Edge System for Health Care Providers.

d
d
d
d
d

- (c) Put processes and procedures in place to ensure the following verifications and reporting requirements are complete :
 - (i) Verify the prescriber is certified and the patient is enrolled in the Clozapine REMS Program prior to dispensing clozapine,
 - (ii) Verify the ANC is current (within 7 calendar days of the blood draw),
 - Verify the ANC is within the acceptable range describe in the Prescribing Information or the prescriber has authorized the continuation of clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits exceed the risks of developing severe neutropenia prior to dispensing clozapine, and
 - Report dosing information for each clozapine prescription/fill to the Clozapine REMS Program.
- () Maintain appropriate documentation that all processes and procedures are in place and are being followed for the Clozapine REMS Program and provide it upon request to the Clozapine Sponsors, FDA, or a third party.
- (e) Comply with audits by the Clozapine Sponsors, FDA, or a third party to ensure that all processes and procedures are in place and are being followed for the Clozapine REMS Program.

d
d
d
d
d

b) As a condition of certification:

(1) Outpatient pharmacies:

- (a) That support electronic communication verification with the Clozapine REMS Program system must:
 - (i) Ensure the pharmacy enables its pharmacy management system to support communication with the Clozapine REMS Program system using established telecommunication standards and runs the standardized validation test transaction(s) to validate the system enhancements.
 - (ii) Dispense clozapine to a patient only after obtaining a pre-dispense authorization by processing all clozapine

d

prescribers include cash claims through the pharmacy management system electronically: M

M

(a) Verify the prescriber's certification of the patient's eligibility for the REMS Program. M

M

(b) Verify the ANC's current withdrawal acceptable range described in the Prescriber Information Manual for the prescriber has authorized the medication for the patient's use. If the patient's ANC falls below the acceptable range when the prescriber determines the benefits exceed the risks of development of severe euphoria. M

M

(c) Reproductive information for each patient's prescriber/family for the REMS program. M

M

(b) Do NOT support electronic medication verification with the REMS Program system. Use the patient's medication after a medication-specific access to the REMS Program website or call the REMS Program customer service: M

M

() Verify the prescriber's certification of the patient's eligibility for the REMS Program. M

M

() Verify the ANC's current withdrawal acceptable range described in the Prescriber Information Manual for the prescriber has authorized the medication for the patient's use. If the patient's ANC falls below the acceptable range when the prescriber determines the benefits exceed the risks of development of severe euphoria. M

M

() Reproductive information for each patient's prescriber/family for the REMS Program. M

M

(2) Medication management: M

M

(a) Use the patient's medication after access to the REMS Program website or call the REMS Program customer service. Verify the prescriber's certification of the patient's eligibility for the REMS Program. M

(b) Do not support medication verification with the REMS Program website or call the REMS Program customer service to check the patient's medical record. Verify the ANC's current withdrawal acceptable range described in the Prescriber Information Manual for the prescriber has authorized the medication for the patient's use. M

continuation of clozapine treatment for patients with an ANC that is below the acceptable range when the prescriber determines the benefits exceed the risks of developing severe neutropenia.

b) Clozapine Sponsors must:

- (1) Ensure that pharmacies that dispense clozapine are specifically certified in accordance with the requirements described above.
- (2) Ensure that the authorized representatives can compete the certification process and pharmacy staffs can compete training online or by fax to the Clozapine REMS Program.
- (3) Ensure that pharmacies are notified when they have been certified in the Clozapine REMS Program.
- (4) Verify every 2 years that the authorized representative's name and contact information corresponds to that of the current designated authorized representative or the certified pharmacy. In addition, require the pharmacy to re-certify with new authorized representative.

The following materials support pharmacy certification:

- *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
- *Knowledge Assessment for Healthcare Providers*
- *Clozapine REMS Pharmacy Enrollment Form*
- *Clozapine REMS Chain Headquarter Pharmacy Enrollment Form*
- Clozapine REMS Program Website

Pharmacy Certification: Issues identified and addressed during the review cycle

Transition process for pharmacy certification

Given the substantial changes to the neutropenia monitoring recommendations and related clozapine treatment algorithms along with modernized requirements adopted in the Clozapine REMS Program compared to the individual registry registries, DRISK determined it was necessary for pharmacies that are registered in one or more of the individual registry registries to engage in certification process of the Clozapine REMS Program. The authorized representative or pharmacy(ies) must 1) review the Guide for Healthcare Providers, 2) successfully complete the Healthcare Provider Knowledge Assessment, and 3) Complete and submit the Pharmacy Enrollment Form, agreeing to implement the program requirements.

As described in Section 4 "Final Transition Plan and Discussion," CPMG will shut down the individual registry registries concurrent with launching the SSSR (30 days post-launch of the Clozapine REMS). The Agency had concerns that this approach does not allow pharmacies to certify in advance of needing to utilize the shared system or patient care.

DRISK raised concern with requiring pharmacies to begin utilizing the Clozapine REMS system or patient management on the same day certification can begin, leaving virtually no time to

certify before needing to interact with the new Clozapine REMS system. CPMG minimized this concern stating that (b) (4), the contracted vendor managing the SSSR, planned 1) direct chain pharmacy engagement and outreach, 2) identification of patients who will need clozapine refilled soon after the SSSR goes live and engagement of the pharmacies that dispense to those patients, and 3) implementation delay of the pre-dispense authorization (PDA) function. DRISK acknowledges that currently clozapine should only be in stock in pharmacies that are registered with one or more of the legacy registries. Pharmacists typically have an established relationship with clozapine prescribers and patients based on how the legacy registries link prescribers with pharmacists. This provides assurance that while compliance may not be optimal initially, patient safety should not be compromised during the transition period. Therefore, the CPMG adequately addressed DRISK concerns.

CPMG conducted an evaluation of clozapine utilization to ensure that resources were being dedicated commensurate with actual clozapine dispensing but, to date, have not shared the details of that evaluation.

- **In-patient pharmacy requirements**

Both inpatient and outpatient pharmacies must be certified in the Clozapine REMS Program. Pharmacies that dispense clozapine to inpatients have different requirements than outpatient pharmacies. Both inpatient and outpatient pharmacies are required to verify the prescriber is certified in the Clozapine REMS Program, the patient is enrolled in the Clozapine REMS Program, and the ANC is current and acceptable according to the patients monitoring algorithm. The main difference between the requirements for the pharmacy types is that outpatient pharmacies obtain an electronic code that is generated by the Clozapine REMS Program if these requirements are met, called a pre-dispense authorization (PDA); whereas, obtaining a PDA is not required before dispensing in an inpatient setting. Obtaining electronic confirmation (i.e., PDA) is not a requirement for inpatient settings because hospitalized patients are under the direct observation of medical professionals who routinely monitor for signs or symptoms of neutropenia and are able to quickly respond and treat a patient who has or is at risk for infection. Moreover, there is increased complexity with implementing a PDA in an inpatient setting. For example, obtaining authorization before every dispensing is overly burdensome especially given that the patient is under the direct medical supervision.

When patients are hospitalized, prescribers continue to be responsible for and are required to report ANC results according to each patient's monitoring frequency and inpatient pharmacies are required to implement the necessary processes and procedures to maintain compliance with the REMS Program to ensure the practitioner who prescribes clozapine is certified and the ANC is current and acceptable (or the prescriber authorizes continued treatment). In addition, it is important the Clozapine REMS Program receive ANCs from hospitalized patients in the event that clozapine patient is hospitalized due to complications from neutropenia.

- **Need for Chain Pharmacy Enrollment Form**

(b) (4) CPMG, indicated that a separate Pharmacy Enrollment Form specific for "chain" pharmacies was recommended based on their experience and it would make certifying chains more efficient (b) (4) planned to outreach directly to all "chain" pharmacies that 1) have a contract relationship established with the switch provider for the Clozapine REMS Program and 2) have enrolled in one or more of the legacy registries.

To minimize potential confusion with regard to which form a pharmacy must complete, DRISK elected to remove mention of the “Chain Headquarters Pharmacy Enrollment Form” from the “Guide for Healthcare Providers” since (b) (4) would be reaching out to the pharmacies directly but include the “Chain Headquarters Pharmacy Enrollment Form” as part of the SSSR.

▪ **Completion of Healthcare Provider Knowledge Assessment**

Given the substantial changes to the neutropenia monitoring recommendations and related clozapine treatment algorithms along with modernized requirements adopted in the Clozapine REMS Program compared to the legacy registries, DRISK determined it was necessary for the authorized representative of a pharmacy to demonstrate understanding of the labeling changes and program requirements as part of the Clozapine REMS Program prescriber certification process. Further, the same knowledge assessment was appropriate for both prescribers and pharmacists because of the integral nature both stakeholders play in their respective requirements.

▪ **Pharmacist training requirements**

DRISK determined it was necessary to require pharmacists who practice in pharmacies with pharmacy management systems that cannot support electronic communication verification of the Clozapine REMS Program requirements must complete the CPMG-provided training (review of the *Guide for Healthcare Providers*) and successfully complete the knowledge assessment. The authorized representative is responsible for providing, confirming completion, and maintaining records of who completed the training. For pharmacists who will dispense clozapine using a pharmacy management system that will incorporate electronic communication verification of the Clozapine REMS Program requirements, the pharmacy may implement training for pharmacists utilizing established training protocols within their pharmacy.

▪ **Pharmacy staff** (b) (4)

CPMG proposed t (b) (4)

(b) (4)

DRISK acknowledges the importance of training staff on the requirements to dispense clozapine in compliance with the Clozapine REMS Program (b) (4)

(b) (4) FDAAA provides FDA the authority to require that, as an element of safe use, *pharmacies* that dispense must be certified and the authorized representative for a pharmacy is responsible for ensuring staff are properly trained. However, given the electronic-based nature of this program, DRISK recognizes that the SSSR must be constructed to ensure the system is compliant with HIPAA technical safeguards. Therefore, to accommodate for pharmacy staff to access the web-based system to obtain a pre-dispense authorization, pharmacy staff (pharmacists or technicians) can create an account to obtain a username and password.

If pharmacy staff do not want to create an account to access the Clozapine REMS Program website to obtain a pre-dispense authorization, staff can also report ANCs and/or obtain a pre-dispense authorization by calling the Clozapine REMS Program call center.

5.2.3 Identification of Safety Conditions

Clozapine will be dispensed with videlicet or other documentation of safety conditions.

- a) To enroll a patient in the Clozapine REMS Program, each prescriber must complete a Clozapine REMS Patient Enrollment Form indicating that the patient or their caregiver has:
 - (1) Been provided *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers* unless clinical judgment indicates that the patient's adherence to the treatment regimen will be negatively impacted by providing *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*
 - (2) Been informed by the prescriber of the risks of clozapine and the Clozapine REMS Program requirements, using *What You Need To Know About Clozapine: A Guide for Patients and Caregivers*.
- b) Clozapine Sponsors must:
 - (1) Ensure that the certified prescriber is able to submit the completed *Clozapine REMS Patient Enrollment Form* online or by fax to the Clozapine REMS Program.
 - (2) Ensure that the certified pharmacy can verify that the prescriber is certified and each patient treated with clozapine is enrolled in the Clozapine REMS Program prior to dispensing (see Section II.A.2).

The following materials support documentation of safety:

- *What You Need To Know About Clozapine: A Guide for Patients and Caregivers*
- *Clozapine REMS Patient Enrollment Form*

Identification of Safety: Issues Identified and Addressed during the Review

▪ Patient Counseling

The individual legacy registries did not include a requirement for the prescriber to counsel the patient on the risk of neutropenia. The REMS Notification Letters to form a SSSR issued in 2012, directed clozapine product manufacturers to include a MG as part of the REMS. However, none of the approved clozapine products include a MG as part of their approved labeling. Furthermore, a MG would likely include information about multiple risks associated with clozapine instead of focusing on the risk that the SSSR is intended to mitigate. After further internal discussion with DPP, DRISK and DPP recommended utilizing an educational tool focused on the risk of neutropenia written for patients to describe, at a minimum, the signs and symptoms associated with neutropenia that a patient or caregiver can recognize, what actions to take if symptoms are recognized, and the need for routine ANC monitoring. "What You Need To Know About Clozapine: A Guide for Patients and Caregivers" provides this information in a patient-friendly format.

5.2.4 Patient Monitoring

Each patient using Clozapine is subject to certain monitoring.

Clozapine Sponsors must ensure that the certified pharmacy can verify the ANC is current and within the acceptable range described in the Prescribing Information or that the prescriber has authorized the continuation of treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits exceed the risks of developing severe neutropenia prior to dispensing clozapine

The following materials support patient monitoring:

- *ANC Lab Reporting Form*
- *Clozapine REMS Website*

Patient Monitoring: Issues identified and addressed during the review cycle

▪ **Neutropenia Monitoring Algorithms**

The SSSR supports and implements the revised labeling for neutropenia by:

- *Only accepting absolute neutrophil count (ANC) results*
- *Implementing a new monitoring algorithm to accommodate for patients diagnosed with BEN*

The Clozapine REMS Program provides prescribers the ability to identify a patient diagnosed with BEN (to distinguish them from the General Population) at the time of initial enrollment or at any point during clozapine treatment.

Once identified as a Patient with BEN in the Clozapine REMS Program, the Clozapine REMS Program provides ANC monitoring and clozapine treatment recommendations specifically designed for Patients with BEN (as outlined in the revised labeling). This prevents unnecessary treatment interruptions or discontinuations that may occur if a Patient with BEN was subject to the ANC monitoring and clozapine treatment recommendations for the General Population.

- *Applying lower ANC thresholds for recommending clozapine treatment interruption or discontinuation*

The Clozapine REMS Program verifies the ANC is current and acceptable, based on the patient's monitoring schedule (i.e., General Population, Patients with BEN), before clozapine can be dispensed to an outpatient. Refer to "Pre-dispense authorization" section for more details.

- *Accommodating for the continuation of clozapine treatment despite moderate to severe neutropenia*

To support the revised labeling, the Clozapine REMS Program allows prescribers to exercise clinical judgment and make a determination about the appropriateness of continuing clozapine treatment based on the totality of a particular patient's health status. Before an outpatient can continue treatment if the ANC continues below 1,000/ μ L (General Population) or 500/ μ L (Patients with BEN), the prescriber is required to provide

a “Treatment Rationale” to document in the Clozapine REMS Program that “the benefits of continuing treatment outweigh the risks of severe neutropenia.”

- *Accommodating for re-initiation (or re-challenge) of clozapine treatment despite previous moderate to severe neutropenia*

The legacy registries do not allow for any patients with ANC less than 1,000/ μ L to restart treatment with clozapine.¹¹ According to the revised labeling, prescribers may rechallenge any patient treated with clozapine who experience moderate or severe neutropenia if the prescriber determines the risk of psychiatric illness is greater than the risk of developing a recurrence of severe neutropenia. The Clozapine REMS Program allows all patients, regardless of previous ANC, to start or re-start clozapine as long as they have a current and acceptable ANC.

The revised labeling eliminates the NNRMF⁵ and it will be discontinued upon the implementation of the Clozapine REMS Program. All available data from all patients who were listed in the NNRMF will be migrated into the Clozapine REMS Program and those patients will be identified with a red flag in the SSSR to alert prescribers who may be considering clozapine again for that patient.

▪ **Pre-dispense authorization**

CPMG’s initial SSSR proposal did not support safe use of clozapine given the labeling changes. The CPMG proposal relied on the prescriber-pharmacist relationship based on the legacy risk management programs and did not provide a centralized communication infrastructure to facilitate information exchange. In particular, without centralized processes in place through the SSSR, it was not clear how a pharmacist would know which patients were diagnosed with BEN, which monitoring algorithm to apply, and where/how to determine if the prescriber authorized continuation of treatment for patients with moderate or severe neutropenia. Confusion could regularly lead to unnecessary treatment interruptions or discontinuations; directly in contradiction of the labeling changes. Furthermore, the prescriber-pharmacist relationship unnecessarily limited a patient’s access to clozapine by limiting patients to filling their clozapine prescription at one pharmacy. In response, CPMG proposed a consistent and centralized process for certified outpatient pharmacies to determine if a patient could be dispensed clozapine based on the Clozapine REMS requirements by using the “pre-dispense authorization” concept. A pre-dispense authorization is an electronic code indicating that the Clozapine REMS Program has verified:

- Patient is enrolled in the Clozapine REMS Program
- Prescriber is certified in the Clozapine REMS Program
- Pharmacy is certified in the Clozapine REMS Program
- ANC is current (reported within 7 days of the blood draw)

¹¹ The Agency is aware that certain legacy registries implemented a “waiver program” in which a prescriber could request a waiver for a patient to restart (or continue) clozapine despite meeting the no-rechallenge criteria. The prescriber is required to provide documentation to the patient registry and the registry makes a determination to grant or deny the waiver request on a case-by-case basis.

- ANC is within an acceptable range, or the prescriber authorized continued treatment

To implement this concept, it requires the ANC result (or the prescriber's authorization to continue clozapine treatment) to be reported to the Clozapine REMS Program *before* clozapine is dispensed to outpatients. Outpatient pharmacies obtain a pre-dispense authorization one of three ways:

- By enabling your pharmacy management system to support electronic communication with the Clozapine REMS Program
- By signing into Clozapine REMS Program website
- By calling the Clozapine REMS Program call center

▪ **Patients under Hospice Care**

The revised labeling addresses hospice patients under “Use in Specific Populations” and states “For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 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.”

To support this labeling provision, the Clozapine REMS Program allows prescriber (b) (4) to identify a patient as a hospice patient to avoid unnecessary laboratory monitoring if the patient is terminally ill.

5.2.5 Patient Enrollment

Each patient using clozapine is enrolled in a registry.

- a) Clozapine Sponsors must ensure that certified prescribers enroll all patients in the Clozapine REMS Program using the *Clozapine REMS Patient Enrollment Form*.
- b) Clozapine Sponsors must maintain a Clozapine REMS registry within the Clozapine REMS Program. The primary objective of the REMS registry is to ensure patient safety and safe use of clozapine through periodic monitoring for severe neutropenia.
- c) Clozapine Sponsors must ensure that patient enrollment can be completed via Clozapine REMS Program website or by fax.

The following materials support Patient Enrollment:

- *Clozapine REMS Patient Enrollment Form*

Patient Enrollment: Issues Identified and Addressed during the Review Cycle

Responsibility of prescriber and patients

The agency registers and enrolls the prescriber or the pharmacist (under certain circumstances) to enroll a patient into a registry. In the SSSR, the prescriber (or prescriber's designated signee) is responsible for enrolling patients because prescribers are responsible for determining if clozapine is the appropriate treatment for the patient, counseling the patient (or caregiver), and determining if the patient has been diagnosed with BEN. e

5.3 Implementation System

1. Clozapine Sponsors must ensure that clozapine is only distributed to certified pharmacists by:
 - a. Ensuring that wholesalers/distributors who distribute clozapine comply with the program requirements for wholesalers/distributors. In order for a wholesaler/distributor to distribute clozapine, the wholesalers/distributors must:
 - i. Put processes and procedures in place to verify, prior to distributing clozapine, that the pharmacists are certified. e
 - ii. Train all relevant staff on the Clozapine REMS Program requirements. e
 - iii. Agree to be audited by the Clozapine Sponsors, FDA, or a third party to ensure that all processes and procedures are in place and are being followed for the Clozapine REMS Program. e
 - iv. Maintain appropriate documentation and make it available for audits. e
 - v. Provide distribution data to the individual Clozapine Sponsors. e
 - b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of clozapine and provide the data to the individual Clozapine Sponsors. e
 - c. Clozapine Sponsors must monitor distribution data and audit the wholesalers/distributors within one year after the wholesaler/distributor is enrolled to ensure that all processes and procedures are in place and functioning to support the requirements of the Clozapine REMS Program. Clozapine Sponsors must institute corrective action if noncompliance is identified. e
2. Clozapine Sponsors must maintain a validated, secure database of pharmacists that are certified to dispense clozapine in the Clozapine REMS Program. e
3. Clozapine Sponsors must maintain adequate records of clozapine distribution, dispensing, certified prescribers, pharmacists, distributors/wholesalers, and patients to meet the REMS requirements. e

4. Clozapine Sponsors must ensure that their practices' REMS requirements are met and may decline to certify noncompliant pharmacists if the requirements do not continue to be met.
5. Clozapine Sponsors must maintain a validated, secure database of patients who are enrolled in the Clozapine REMS Program.
6. Clozapine Sponsors must maintain a Clozapine REMS Program contact center to support prescribers and pharmacists interfacing with the Clozapine REMS Program.
7. Clozapine Sponsors must ensure that all materials listed in or appended to the Clozapine REMS document are available through the Clozapine REMS Program website (www.clozapine.com) or by calling the Clozapine REMS Program contact center.
8. The Clozapine REMS Program website (www.clozapine.com) must continue for the duration of the REMS. The Clozapine REMS Program website must include the option to e-print versions of the Clozapine REMS Program materials. Individual, product-specific clozapine websites for health care professionals must include a prominent REMS-specific link to the Clozapine REMS Program website.
9. Clozapine Sponsors must continuously monitor certified pharmacists to ensure their requirements of the Clozapine REMS Program are being met. Clozapine Sponsors must institute corrective action if noncompliance is identified.
10. Clozapine Sponsors must audit certified pharmacists that have ordered clozapine to ensure that all processes and procedures are in place and functioning to support the requirements of the Clozapine REMS Program on the following schedule:
 - a. Eight percent within one year from the date of initial approval of the REMS
 - b. Eight percent every two years thereafter

Clozapine Sponsors must institute corrective action if noncompliance is identified.

11. Clozapine Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Clozapine REMS Program based on monitoring and evaluation of the Clozapine REMS Program.

Implementation System: Issues identified and addressed during the review cycle

▪ Distributor Enrollment

Distributor Enrollment is addressed in the SSSR to ensure that the distributor requirements are consistently communicated to distributors. CPMG members explained that to modify the existing contracts with distributors would be unduly burdensome to anticipate and negotiating the opportunity the modification would provide. DRISK agreed handling the distribution requirements for clozapine as a separate contract is acceptable to minimize unintended consequences of modifying the existing contracts.

- b) Patient satisfaction by Patient Type (General population, BEN patients, NNRMF 1 patients, hospice patients) 1
- (1) 1 Act v 1
 - (2) 1 I t r r p t d 1
 - (3) 1 D s c o t 1 d 1
2. 1 Contact Center Report 1
- a) Number of Contacts 1
 - b) Summary of reason for call (Examples may include "Enrollment question", "Lab query", etc.) by reporter (. . . pharmacy, prescriber, patient) 1
 - c) Narrative of a corrective action strategy from lessons learned 1
3. 1 Clozapine REMS Program Compliance (to be included beginning with the 12 Month REMS Assessment Report) 1
- a) Alerts 1
 - (1) 1 Summary of additional steps for alerts conducted during reporting period. 1
 - (2) 1 Summary of corrective actions taken to address findings, the status of the corrective actions, a date by which preventive actions that will be taken 1
 - b) Number of clozapine prescriptions dispensed that were written by locum tenens prescribers (reported to CDC through AdT) 1
 - (1) 1 Actions taken (Examples may include "Provision of clozapine program materials", "Prescriber becomes certified", etc.) 1
 - (2) 1 Outcome of actions taken 1
 - c) Number of prescriptions dispensed by locum tenens pharmacist and actions taken to prevent further occurrences (reported to CDC through AdT) 1
 - d) Number of shipments sent to locum tenens pharmacist, so recall of report, and actions taken to prevent further occurrences 1
 - (1) 1 Number of times a clozapine prescription was dispensed by a pharmacy bypassed REMS alerts and if a physician's occurrence was described, how the physician would be notified, the root cause of the failure, a date by which corrective actions taken (reported to CDC through AdT). Justify by pharmacy type (inpatient or clozapine system PDA) 1
 - f) Non-compliance with the Clozapine REMS Program requirements, so recall of report, a date by which corrective action resolved 1
 - (1) 1 Number of PDAs without ANC (excluding hospice patients) and number of physicians reporting clozapine dispensed 1
 - (2) 1 Number of PDAs without treatment that also provided with ANC 1
 - accptabl, and number of the physicians reporting clozapine dispensed 1
4. 1 Barriers or Delays to Patient Access 1
- a) False statements: e.g., all listed barriers corrected, but system still reported as 1
 - prescription rejected 1
 - b) If identified enrollment activities, or failures to identify enrollment for forthcoming enrollment reports 1

- c) : Repo e : ck of ce ifie p esc ibe s n /o ph :m æies in p ien 's oc : e :
-) : Unin en e sys em in e up ions n : eso u ions :
- e) : Fo PDAs vi e ec onic ve ific ion Numbe of imes n : e sons :m au :b ck- :
up sys em w :s use :o v :i :e :p esc ip ion :n :sou ce of p ob em (e.g., swi ch :
eve , ph :m æy: eve ,REMS : b se, e c) :

- 5. : In pp op i eP :ien Access :
 -) Inp :ien ph :m æy ispsensing fo ou p :ien use (epo e o : e ec e :h ough u i) :
 - b) F :se posi ves :e.g., one o : en i ies we e no :ce ifie :bu :sys em:ve ifie :
ispsensing/gene :e : PDA :

B. Evaluation of Safe Use Behaviors :

- 1. : P esc ip ion Rejec ions :
 -) : Numbe :of p e- ispsense :u ho iz ions (PDAs) :h : i :no :encoun e : ny :
REMS- :e :e :ejec ions p io :o being u ho ize :
 - b) : To : numbe of u ho iz :ions h :encoun e e :nyREMS- e :e :ejec ions :
 - c) : Me n n :me i n n : nge of u :ion of ime o u ho ize :
) : P ovi e :e sons fo :p esc ip ion :ejec ions s : ifie : by :ype of PDA :(vi :
ph :m æy :m n gemen :sys em:o c oz pine REMS) :n : u :ion of ime o :
u ho ize p esc ip ion ifini i :y eiec e :
- 2. : T e :men R :ion :es :
 -) : Numbe of æ :men : ion :es submi e ,s : ifie :by ype :
 - b) : Me n numbe of e :men : ion :es submi e pe p esc ibe ' :
- 3. : Numbe of no ific ions n : e s sen ,s : ifie by ype n :s keho :e ype :
(P esc ibe , Ph :m æy) :

C. Evaluation of Knowledge/Surveys :

- 1. : An ev :u :tion of know e ge of ce ifie :p esc ibe s of he :isk of seve e :
neu openi , :pp op i e moni o ing of c oz pine, n :REMS equi emen s :
- 2. : An ev :u :tion of know e ge of u ho ize :ep esen :ives, ph :m æis s of he isk of :
seve e neu openi , pp op i e moni o ing of c oz pine, n :REMS equi emen s :
- 3. : An ev :u :tion of know e ge of p :ien s o c :egive s of he isk of seve e neu openi , n :
pp op i e moni o ing of c oz pine :

D. Evaluation of Required Monitoring :

- 1. : To : ins nces of seve e neu openi fo unique p :ien s (epo e : s owes ANC fo :
e ch unique p :ien whose ANC is less than 500/ μ L wi hin e ch mon h) :
- 2. : To : ins nces of neu openi fo unique p :ien s (epo e : s owes ANC fo e ch :
unique p :ien whose ANC is ess h n 1500/ μ L wi hin e ch mon h) :

- E. : With respect to each goal included in the REMS, an assessment of the extent to :
which the approved REMS, including each element of the REMS, is meeting the :
goal or whether one or more such goals or such elements should be modified. :**

**F. Clozapine REMS Program Transition Status (to be included in the 6 Month 6
REMS Assessment Report n y) 6**

1. 6 Date when REMS materials became available to healthcare professionals on 6
the website and via the contact center 6
2. 6 Dates healthcare professionals could become certified online, by mail, and by fax 6
3. 6 Automatic data transition: 6
 - a) 6 Total number of prescribers automatically transitioned into the Clozapine 6
REMS Program (i.e. who were associated with a patient with a valid ANC or 6
WBC lab value within the past 3 years), and date the transition was completed 6
 - b) 6 Total number of prescriber designees automatically transitioned into the 6
Clozapine REMS Program (i.e. who were associated with a patient with a valid 6
ANC or WBC lab value within the past 3 years), and date the transition was 6
completed 6
 - c) 6 Number of pharmacies automatically transitioned into the Clozapine REMS 6
Program (i.e. who were associated with a patient with a valid ANC or WBC lab 6
value in one or more of the individual clozapine patient registries within the past 6
3 years), and date the transition was completed 6
 - d) 6 Total number of patients transferred into the Clozapine REMS Registry (must 6
have a valid ANC or WBC lab value in one or more of the individual clozapine 6
patient registries within the past 3 years) 6
 - e) 6 Number of patients automatically transitioned into the Clozapine REMS 6
Registry who previously were on the National Non-Rechallenge Master File 6
(NNRMF), and the number that have been flagged as such in the Registry 6
 - f) 6 Dates individual clozapine patient registry websites began redirecting visitors to 6
the Clozapine REMS Program 6

**G. Clozapine REMS Program Outreach and Communication (to be included in 6
the 6 nd 12 Month 6 REMS Assessment Report n y) 6**

1. 6 Dates of distribution of the Dear HCP Letter, Dear Distributor Letter, Dear 6
Professional Society Letter and the numbers sent on each date. Provide a list of the 6
documents included with each distribution including the revision date. 6
2. 6 Number of undeliverable and returned communications for each distribution date, by 6
method of distribution 6
3. 6 A summary of the Clozapine REMS Program website utilization 6

**H. Knowledge Assessments (to be included in the 6 nd 12 Month 6
REMS 6
Assessment Report n y) 6**

1. 6 Number of completed Knowledge Assessment for Healthcare Providers (KAs) for 6
certified prescriber and pharmacy authorized representative, and pharmacy staff that 6
have elected to take the KA, including method of enrollment and number of attempts 6
to complete, by stakeholder 6
2. 6 Summary of the most frequently missed KA questions, stratified by prescriber and 6
pharmacy 6
3. 6 A summary of potential comprehension or perception issues identified with the KA 6

4. v Pro o v r v iation for Cloza in van th vRi k of N vtro vnia: A Gui vfor v H valthcar Pro i v an /or th vKnowl v v v nt for H valthcar Pro i v v S vth v v n v tabl v lo v by DRISK REMS A v nt T a vto a v t CPMG v in th vorganizing th vREMS a v nt ata. v

Issues related to REMS Assessment v

▪ vANDA participation v

All v b r (NDA an vANDA v nufactur r) of th vCPMG int n sto vartici at with v th vREMS A v nt . v

5.6 v VETERAN'S HEALTH ADMINISTRATION (VA) v

(b) (4)

(b) (4), CPMG vr vnt va vo o al tha (b) (4)

DRISK wa vconc rn v about thi vro o a (b) (4)

On Augu t 4, 2015, FDA al rt vCPMG that w vha v significant conc rn with th v ro o v lan (b) (4) In a vition, FDA vx lain v thi i u will not furth r i vact a vro al an vFDA i acti vly v loring th v v t ath v forwar v (b) (4)

(b) (4)

¹³ Eav il co w vnication Augu t 4, 2015 to Su an Ku v r r. Sign v in DARRTS on Augu t 14, 2015 by v Flow r L. v

(b) (4)

(b) (4)

In addition, VA is advised that

they intend to be part of the SSSR to ensure that patient information is available through the Clozapine REMS Program patient management system. From the VA's perspective, the issues of compliance are related more to the technical aspects of data information exchange and necessary interfacing with the Clozapine REMS Program.¹⁴

(b) (4)

(b) (4)

At the time of finalizing his review, FDA continues to explore how WPA will be incorporated into the SSSR and what, if any, REMS modifications may be needed to ensure VA is in compliance with the SSSR requirements. FDA intends to resolve these issues with VA and CPMG during the transition period.

6 CONCLUSION AND RECOMMENDATIONS

In conclusion, the proposed SSSR submitted September 14, 2015 incorporates all clozapine products under a shared program to provide a centralized point of communication for prescribers and pharmacists; and supports the updated labeling change to accommodate for the treatment of patients with BEN and capture a prescriber's decision to continue clozapine treatment when the prescriber determines that the benefits outweigh the risk of severe neutropenia.

FDA will continue to work with CPMG and VA to ensure VA is in compliance with the SSSR requirements and require modifications to the REMS if needed to address this issue.

The proposed Clozapine REMS is appended materials and the SSSR Supporting Document submitted by the CPMG on September 14, 2015 is acceptable. DRISK recommends approval of the Clozapine REMS appended to his review.

7 ATTACHMENTS/APPEDED INFORMATION

234 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

¹⁴ VA/FDA teleconference occurred in accordance with MOU 05-08-03.

¹⁵ Memorandum of Meeting Minutes for the August 1, 2015 teleconference between FDA and VA. Signed in DARRTS on September 3, 2015 by Ayala Somayajula V.

----- R
This is a research article that has been
I originally published in his journal. I
signed it. R

----- R
/s/ R
----- R

KIMBERLY LEHFFELD R
09/14/2015 R
concur with Suzanne Bottom's review. R

EEMA J MEHTA R
09/14/2015 R
I concur. R

CYNTHIA L LACIVITA R
09/14/2015 R
I concur R

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS)

Date: September 3, 2015

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.
Health Communications Analyst
(DRISK)

Kate Oswell, M.A.
Health Communications Analyst
(DRISK)

Team Leader: Kim Lehrfeld, Pharm.D.
DRISK

Deputy Division Director:
(Acting) Reema Mehta, Pharm.D.
DRISK

Subject Review of CPMG's August 14, 2015 proposed Single Shared System REMS, August 24, 2015 follow-up issues from FDA/CPMG August 20, 2015 teleconference, and August 28, 2015 proposed screenshots

Drug Name(s): Clozapine

Therapeutic Class: atypical antipsychotic

Dosage and Route: oral

Drug	Application Number	Applicant	Date Received	eCTD Sequence #/ Supporting doc
Clozaril	NDA 019758	Novartis	09/04/2015	0072/470

Clozapine	ANDA 202873	Accord	09/03/2015	0015/16
	ANDA 074949	Teva	09/04/2015	0013/346
	ANDA 076809		09/04/2015	0012/190
	ANDA 203039		09/04/2015	0013/15
	ANDA 90308		09/04/2015	0007/36
	ANDA 075417	Mylan	09/03/2015	0039/137
	ANDA 201824		09/03/2015	0025/29
	ANDA 075713	Caraco/Sun	09/08/2015	0016/127
ANDA 203807	Actavis/Watson	09/04/2015	0019/20	
Fazaclo ODT	NDA 021590	Jazz	09/04/2015	0022/347
Versacloz	NDA 203479	Jazz	09/04/2015	0069/102

OSE RCM #: 2014-2345

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This is a review of the Clozapine Product Manufacturers Group (CPMG) revised proposed risk evaluation and mitigation strategy (REMS) for a single shared system REMS (SSSR) submitted via email on August 14, 2015. The same proposed SSSR was submitted in parallel to the individual NDA and ANDA applications.

A comprehensive review of the regulatory history and rationale for the design of the SSSR will be documented in a subsequent review.

2 MATERIALS REVIEWED

CPMG's proposed SSSR. Submitted via email on August 14, 2015. The submission includes the following materials:

1. REMS Document
2. REMS Supporting Document
 - Distributor Enrollment Form
 - Transition Plan Materials
 - Dear Pharmacy Letter wave 1
 - Dear Pharmacy Letter wave 2
 - Dear Pharmacy Letter wave 3
 - Dear Prescriber Letter wave 1
 - Dear Prescriber Letter wave 2
 - Dear Prescriber Letter wave 3
 - Dear Professional Society – Pharmacy
 - Dear Professional Society – Prescriber
 - “What’s New with Clozapine” Overview
3. Guide for HCPs
4. Knowledge Assessment for HCPs
5. Knowledge Assessment for Prescriber Designees
6. Education Program for Prescriber Designees
7. Guide for Patients and Caregivers
8. Chain Headquarter Pharmacy Enrollment Form
9. Pharmacy Enrollment Form
10. Pharmacy Staff Attestation Language
11. Prescriber Enrollment Form
12. Prescriber Designee Enrollment Form
13. Patient Enrollment Form
14. ANC Lab Reporting Form

In addition to the proposal submitted on August 14, 2015:

- On August 24, 2015, via email, CPMG submitted follow-up to issues discussed during the August 20, 2015 CPMG/FDA teleconference regarding pharmacist training, use of the word “registry” on the Clozapine REMS Program website, and screenshots of the “eligibility check” and “predispose authorization” screenshots
- On August 28, 2015, via email, CPMG submitted the website screenshots

The following materials were revised and sent to the CPMG via email on September 1, 2015. The revised materials are attached to this review:

1. **REMS Document and attachments**
 2. Prescriber Enrollment Form
 3. Prescriber Designee Enrollment Form
 4. Chain Headquarters Pharmacy Enrollment Form
 5. Pharmacy Enrollment Form

6. Patient Enrollment Form
7. ANC Lab Reporting Form
8. Knowledge Assessment for HCPs
9. Guide for Patients and Caregivers
10. Distributor Enrollment Form
11. Dear Prescriber Letters – wave 1
12. Dear Prescriber Letter – wave 2
13. Dear Prescriber Letter – wave 3
14. Dear Pharmacist Letter – wave 1
15. Dear Pharmacist Letter – wave 2
16. Dear Pharmacist Letter – wave 3
17. Dear Professional Society Letter – Pharmacy
18. Dear Professional Society Letter – Prescriber
19. What’s New with Clozapine – An Overview
20. Prescriber Designee Education Program
21. Prescriber Designee Knowledge Assessment
22. Pharmacy staff attestation language

Note: Comments in Section 4 “Comments For The CPMG sent September 1, 2015” of this review were sent via email with these materials on September 1, 2015.

The following materials were revised and sent to CPMG via email on September 3, 2015. The marked-up materials are attached to this review.

- Guide for HCPs
- REMS Supporting Document
- FDA Response CPMG Follow-Up proposal on issues discussed during the August 20, 2015 teleconference
- Screenshots (submitted August 28, 2015)

Note: Comments in Section 5 “Comments For The CPMG sent September 3, 2015” of this review were sent via email with these materials on September 3, 2015.

FDA Responses to the issues outlined in the slide set CPMG submitted on August 24, 2015 regarding pharmacist training, use of the word “registry” on the Clozapine REMS Program website, and screenshots of the “eligibility check” and “predispense authorization” screenshots were also sent to CPMG via email on September 3, 2015.

2.1 OTHER DRISK REVIEWS

- The following review was completed for the proposed SSSR submitted on June 26, 2015 (Round 4)
 - Robottom S. DRISK review signed in DARRTS on August 5, 2015 by Lehrfeld K.

- The following review was completed for the proposed SSSR submitted on April 17, 2015 (Round 3)
 - Robottom S. DRISK review signed in DARRTS on August 4, 2015 by Lehrfeld K.
- The following review was completed for the proposed SSSR submitted on December 23, 2014. (Round 2)
 - Robottom S. DRISK review signed in DARRTS on June 19, 2015 by Lehrfeld K.
- The following reviews were completed for the initial proposed SSSR submitted on September 18, 2014 (Round 1)
 - Robottom S. DRISK review signed into DARRTS on November 19, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 3, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 19, 2014 by Lehrfeld K.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Clozapine SSSR proposal be sent to the applicant.

4 COMMENTS FOR THE CPMG SENT SEPTEMBER 1, 2015

The following materials we have no comments/revisions and consider them final:

1. Prescriber Enrollment Form
2. Prescriber Designee Enrollment Form
3. Chain Headquarters Pharmacy Enrollment Form
4. Pharmacy Enrollment Form
5. Distributor Enrollment Form
6. Prescriber Letter – wave 2
7. Prescriber Letter – wave 3
8. Pharmacy Letter – wave 3

The final materials we have minor comments/edits and consider them final if all the revisions are addressed:

9. REMS Document
10. Patient Enrollment Form
11. ANC Lab Reporting Form
12. HCP Knowledge Assessment
13. Designee Knowledge Assessment
14. Designee Education
15. Pharmacy Staff Attestation

16. Guide for Patients and Caregivers
17. Prescriber Letter – wave 1
18. Pharmacy Letter – wave 1
19. Pharmacy Letter – wave 2
20. Professional Society – Pharmacy
21. Professional Society – Prescriber
22. What’s New with Clozapine

- Comments on the Guide for HCPs and REMS Supporting Document will be provided under separate cover.
- For each piece listed above, please respond in writing if you accept the FDA edits. If you do not accept the revisions, resubmit the revised piece (via email) for review. In addition, via email only, please resubmit the following revised pieces for review as soon as possible (and in advance of 9/8 final submission):
 - HCP Knowledge Assessment
 - What’s New with Clozapine
- In addition, before the final 9/8 submission, in a separate Word document, submit (via email) a “List of Applicants.” Include the following information - manufacturer name, NDA/ANDA number, and product name. Please submit the “list of applicants” document at your earliest convenience for FDA to review.
- The website screenshots (submitted 8/28) are under review and comments will be provided under separate cover.
- Comments on the Outstanding Issues (Follow-Up to 8/20 teleconference) will be addressed under separate cover.

4.1 RESUBMISSION REQUIREMENTS AND INSTRUCTIONS

Resubmission Requirements and Instructions: For the final 9/8 submission, provide a separate, clean MS Word version of each document, form, or material, including the “List of Applicants” requested above. If you are not able to provide a particular document, form, or material in Word, submit it only as a PDF.

In addition, provide the following in a single, combined PDF:

- 1. REMS Document**
2. Prescriber Enrollment Form
3. Prescriber Designee Enrollment Form
4. Chain Headquarters Pharmacy Enrollment Form
5. Pharmacy Enrollment Form
6. Patient Enrollment Form
7. ANC Lab Reporting Form
8. Guide for HCPs
9. Knowledge Assessment for HCPs
10. Guide for Patients and Caregivers

In a separate PDF from the above listed materials, provide the following in a single, combined PDF:

11. **REMS Supporting Document**
12. Distributor Enrollment Form
13. Pharmacy Staff Attestation Language
14. Prescriber Designee Education Program
15. Prescriber Designee Knowledge Assessment
16. Dear Prescriber Letters – wave 1
17. Dear Prescriber Letters – wave 2
18. Dear Prescriber Letters – wave 3
19. Dear Pharmacist Letter – wave 1
20. Dear Pharmacist Letter – wave 2
21. Dear Pharmacist Letter – wave 3
22. Dear Professional Society Letter – Prescriber
23. Dear Professional Society Letter - Pharmacy
24. What’s New with Clozapine – An Overview
25. Website – transition screenshots

Please note the website is not fully accounted for in the above lists. FDA will provide further guidance on how to append the website under separate cover.

5. COMMENTS TO THE CPMG SENT SEPTEMBER 3, 2015

Track-changes and comments on the following pieces were provided:

- REMS Supporting Document

In addition, the following remaining outstanding issues – follow-up to the 8/20 teleconference (and provided to FDA on August 24, 2015) were addressed:

5.1 Pharmacist Training

CPMG Proposal: CPMG considers it the role of the authorized representative of the pharmacy *to conduct and track completion* of any individual pharmacist training at their location. To enable this, CPMG proposes at the time the authorized representative receives confirmation of completion of the certification requirements, the Clozapine REMS Program will provide the authorized representative links to PDFs of the Guide for Healthcare Providers, Knowledge Assessment for Healthcare Providers, and the answer key for the Knowledge Assessment for Healthcare Providers. In this communication, the authorized representative will be reminded of his/her responsibility to train and maintain records of pharmacist training at their location.

CPMG proposes to add the following instructions on the Pharmacy Certification Confirmation Page:

Please download the [REDACTED] (b) (4)
[REDACTED] the Knowledge Assessment from [REDACTED] (b) (4)

(b) (4) These tools should be used to train all pharmacists and relevant staff involved in dispensing clozapine. (b) (4)

A record of the training must be maintained for future review by the Clozapine REMS Program.

FDA Response: The proposal is acceptable.

We note that page 23 of the “Annotated CPMG website screen captures_5_2015-08-22_v2” present the “Pharmacy Certification Confirmation” with the text “Your pharmacy is now certified in the Clozapine REMS Program.” Please confirm if this is the correct screenshot. It seems the authorized representative confirmation page is more appropriate for this information [please reference “6.4 Authorized Representative Confirmation” (page 47, 5.8.2015 screen captures)].

5.2 Use “Registry” on the Clozapine REMS Program website

CPMG Proposal: CPMG will update the screenshot submission document for submission #5 (due to FDA on 8/28) to reflect these changes; however, technical implementation of these changes will occur after approval.

The approvable materials will align with FDA expectations, and the website changes will be made in the first release, which would be in the first 30 days post-go-live (i.e., 60 days post approval).

FDA Response: The proposal is acceptable. See revisions to reflect this agreement in the REMS Supporting Document.

5.3 Eligibility Check and Predispose Authorization (PDA) screenshots

CPMG Proposal: The eligibility check will be the only option for selection from web dashboards for prescribers, prescriber designees, pharmacy authorized representatives, and pharmacy staff (for both inpatient and outpatient pharmacies) for Phase 2 (Oct 12 through Dec 14) to allow any stakeholder to check eligibility before PDA functionality is available.

The eligibility check fields have been updated to not require manufacturer and NDC, knowing that these may not be fields that prescribers or their designees may have or know.

At PDA launch (Dec 14) , prescribers, prescriber designees, authorized representatives and pharmacy staff for **inpatient** pharmacies will only have the option to access patient eligibility check from their dashboard (not PDA). For consistency, functionality has been provided to both Prescribers and Prescriber Designees.

At PDA launch (Dec 14), authorized representatives and pharmacy staff for **outpatient** pharmacies will only have the option to access patient PDA request from their dashboard (not eligibility).

Instructions on the Prescriber and Prescriber Designee Eligibility Check Screens have been updated to clearly explain the purpose of the eligibility check.

FDA Response: FDA reviewed the above proposal and the 24 screenshots provided on 8/24. The proposal is acceptable with the following comments below. Refer to the revisions to reflect this agreement in the REMS Supporting Document.

- Page 24 – 3. Prescriber Dashboard – Eligibility check [see also 8/28/15 screenshots, Part 4, pages 16, 31, 38, and 54]
 - Clarify if the instructional paragraph as written (8/24 submission, 3. Prescriber Dashboard, page 24 and 8/28 submission Part 4, page 16) will appear during Phase 2 (Oct 12 through Dec 14) or if a modified version will appear. As written, it states (b) (4)
 - 2. Revise or remove this statement to avoid confusion.

Further, after Phase 2, it may be confusing for prescribers/designees since it states that (b) (4) Should this statement be revised to state, “This Eligibility Check is only intended to determine if the safe use conditions have been met for your inpatient to receive clozapine.”?
 - Please clarify if each data element of the dispensing information is optional or if only the manufacturer and NDC are optional. Based on the screenshot, “(opt)” appears in each field (i.e., date of service, manufacturer, NDC#, Days Supply, Quantity) which is acceptable.
- Page 26 – 4. Prescriber Designee Dashboard – Eligibility Check [see also 8/28/15 screenshots, Part 4, page 38]
 - We note that the Prescriber Designee Dashboard – Eligibility Check screenshot submitted on 8/24 is different from the screenshot submitted on 8/28 (Part 4, page 38). Please explain which text is correct and revise as appropriate to address the above comments.

5.4. Website

Attach the entire, final version of the website screenshots to the REMS Document. Therefore, provide the following in a single, combined PDF:

1. **REMS Document**
2. Prescriber Enrollment Form
3. Prescriber Designee Enrollment Form
4. Chain Headquarters Pharmacy Enrollment Form
5. Pharmacy Enrollment Form
6. Patient Enrollment Form
7. ANC Lab Reporting Form
8. Guide for HCPs
9. Knowledge Assessment for HCPs
10. Guide for Patients and Caregivers

11. Website screenshots (final version)

Do not append any transition screenshots to the REMS Document or to the REMS Supporting Document.

ATTACHMENTS

- **REMS Document**
- Prescriber Enrollment Form
- Prescriber Designee Enrollment Form
- Chain Headquarters Pharmacy Enrollment Form
- Pharmacy Enrollment Form
- Patient Enrollment Form
- ANC Lab Reporting Form
- Guide for HCPs
- Knowledge Assessment for HCPs
- Guide for Patients and Caregivers
- **REMS Supporting Document**
- Distributor Enrollment Form
- Pharmacy Staff Attestation Language
- Prescriber Designee Education Program
- Prescriber Designee Knowledge Assessment
- Dear Prescriber Letters – wave 1, 2, and 3
- Dear Pharmacist Letter – wave 1, 2, and 3
- Dear Professional Society Letter – Prescriber
- Dear Professional Society Letter - Pharmacy
- What’s New with Clozapine – An Overview
- Website screenshots

300 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY LEHRFELD

09/11/2015

Entered for Suzanne Robottom, Pharm.D.

I concur.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS)

Date: July 31, 2015

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.
Health Communications Analyst
(DRISK)

Kate Oswell, M.A
Health Communications Analyst
(DRISK)

Team Leader: Kim Lehrfeld, Pharm.D.
DRISK

Deputy Division Director:
(Acting) Reema Mehta, Pharm.D.
DRISK

Subject: Review of CPMG's June 26, 2015 proposed Single
Shared System REMS and July 10, 2015 proposed
screenshots

Drug Name(s): Clozapine

Therapeutic Class: atypical antipsychotic

Dosage and Route: oral

Drug	Application Number	Applicant	Date Received	eCTD Sequence #/ Supporting doc
Clozaril	NDA 019758	Novartis	07/17/15	0067/464
Clozapine	ANDA 202873	Accord	7/16/15	0012/13

	ANDA 074949	Teva	07/17/15	0010/341
	ANDA 076809		07/17/15	0009/185
	ANDA 203039		07/17/15	0011/13
	ANDA 90308		07/17/15	0005/34
	ANDA 075417	Mylan	07/17/15	0035/133
	ANDA 201824		07/17/15	0021/25
	ANDA 075713	Caracco/Sun	07/15/15	0012/123
	ANDA 203807	Actavis/Watson	07/13/15	0017/18
Fazaclo ODT	NDA 021590	Jazz	07/17/2015	0020/342
Versacloz	NDA 203479	Jazz	07/17/2015	0065/98

OSE RCM #: 2014-2345

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This is a review of the Clozapine Product Manufacturers Group (CPMG) revised proposed risk evaluation and mitigation strategy (REMS) for a single shared system REMS (SSSR) submitted via email on June 26, 2015. The same proposed SSSR was submitted in parallel to the individual NDA and ANDA applications.

A comprehensive review of the regulatory history and rationale for the design of the SSSR will be documented in a subsequent review.

2 MATERIALS REVIEWED

CPMG's proposed SSSR. Submitted via email on June 26, 2015. The submission includes the following materials:

1. REMS Document
2. REMS Supporting Document
 - Distributor Enrollment Form
 - Transition Plan Materials
 - Dear Pharmacy Letter wave 1
 - Dear Pharmacy Letter wave 2
 - Dear Pharmacy Letter wave 3
 - Dear Prescriber Letter wave 1
 - Dear Prescriber Letter wave 2
 - Dear Prescriber Letter wave 3
 - Dear Professional Society – Pharmacy
 - Dear Professional Society – Prescriber
 - “What’s New with Clozapine” Overview
3. Guide for HCPs
4. Knowledge Assessment for HCPs
5. Knowledge Assessment for Prescriber Designees
6. Education Program for Prescriber Designees
7. Guide for Patients and Caregivers
8. Chain Headquarter Pharmacy Enrollment Form
9. Pharmacy Enrollment Form
10. Pharmacy Staff Attestation Language
11. Prescriber Enrollment Form
12. Prescriber Designee Enrollment Form
13. Patient Enrollment Form
14. ANC Lab Reporting Form

In addition to the proposal submitted on June 26, 2015, on July 10, 2015, via email CPMG submitted the Clozapine REMS Program website screenshots and a slide set of 6 points of disagreement regarding FDA feedback on the screenshots previously reviewed.

The following materials were revised and sent to CPMG via email on July 31, 2015. The marked-up materials are attached to this review.

- Website screenshots

Note: Comments in Section 5 “Comments For The CPMG sent July 31, 2015” of this review were sent via email with these marked-up screenshots on July 31, 2015.

The following materials were revised and sent to the CPMG via email on July 22, 2015. The revised materials are attached to this review:

1. **REMS Document and attachments**
 2. Prescriber Enrollment Form
 3. Prescriber Designee Enrollment Form
 4. Chain Headquarters Pharmacy Enrollment Form
 5. Pharmacy Enrollment Form
 6. Patient Enrollment Form
 7. ANC Lab Reporting Form
 8. Guide for HCPs
 9. Knowledge Assessment for HCPs
 10. Guide for Patients and Caregivers
11. **REMS Supporting Document and attachments**
 12. Distributor Enrollment Form
 13. Dear Prescriber Letters – wave 1
 14. Dear Prescriber Letter – wave 2
 15. Dear Prescriber Letter – wave 3
 16. Dear Pharmacist Letter – wave 1
 17. Dear Pharmacist Letter – wave 2
 18. Dear Pharmacist Letter – wave 3
 19. Dear Professional Society Letter – Pharmacy
 20. Dear Professional Society Letter – Prescriber
 21. What’s New with Clozapine – An Overview
 22. Prescriber Designee Education Program
 23. Prescriber Designee Knowledge Assessment
 24. Pharmacy staff attestation language
25. FDA Response to “Submission #3 website screenshots feedback response” slide set

Note: Comments in Section 4 “Comments For The CPMG sent July 22, 2015” of this review were sent via email with these materials on July 22, 2015.

FDA Responses to the points of disagreement in the slide set titled “Submission #3 website screenshots feedback response” were also sent to CPMG on July 22, 2015. FDA responses were embedded in the slide set.

The proposed Important Safety Information was reviewed by the Office of Prescription Drug Promotion and comments were sent to CPMG on July 6, 2015. DRISK agreed with OPDP review.

2.1 OTHER DRISK REVIEWS

- The following review was completed for the proposed SSSR submitted on April 17, 2015 (Round 3)
 - Robotom S. DRISK review signed in DARRTS on August 4, 2015 by Lehrfeld K.

- The following review was completed for the proposed SSSR submitted on December 23, 2014. (Round 2)
 - Robottom S. DRISK review signed in DARRTS on June 19, 2015 by Lehrfeld K.
- The following reviews were completed for the initial proposed SSSR submitted on September 18, 2014 (Round 1)
 - Robottom S. DRISK review signed into DARRTS on November 19, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 3, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 19, 2014 by Lehrfeld K.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Clozapine SSSR proposal be sent to the applicant. Please request that the applicant resubmit the revised REMS (i.e., REMS Document and all REMS materials) and Supporting Document as soon as possible to facilitate further review.

4 COMMENTS FOR THE CPMG SENT JULY 22, 2015

4.1 REMS DOCUMENT

- A. As the REMS Document is reviewed within the Agency, additional revisions have been made. We find the revisions to be minor and editorial in nature; not fundamentally changing any aspect of the program or REMS Document. The edits are in track changes along with comments. If these edits are accepted, we believe we are in agreement with a final REMS Document.
- B. See revised REMS Document.

4.2 REMS MATERIALS

We attempted to revise the materials to illustrate formatting/spacing. However, tables, coloring, and formatting may have shifted in transition.

We find the revisions we provided to be clarifying and are not intended to fundamentally change aspects of the program. Rather, the materials were reviewed considering first the intended purpose of the piece and then revised to be as clear, constructive and as concise as possible while adequately explaining various requirements and functions. If you identify that revisions fundamentally change the program design, identify those revisions so we can further discuss.

Once the edits are accepted and the comments are addressed, we consider these materials final.

4.2.1 Prescriber Enrollment Form

See Prescriber Enrollment Form. No comments.

4.2.2 Prescriber Designee Enrollment Form

See revised Prescriber Designee Enrollment Form. One minor comment.

4.2.3 Pharmacy Enrollment Form

See revised Pharmacy Enrollment Form. Three minor edits in the “For Outpatient Only” section and “Authorized Representative Information” section.

The safe use conditions are outlined in Attestation Bullet #5, not #12. The PDA represents the verification of the safe use conditions but does not explain them. Revise the “no” option to state “as outlined in attestation #5” (not #12). If you disagree, provide your rationale and request a teleconference.

4.2.4 Chain Headquarters Pharmacy Enrollment Form

See revised Pharmacy Enrollment Form. Two minor edits in the “Authorized Representative Information” section.

4.2.5 Patient Enrollment Form

See revised Patient Enrollment Form. Three minor edits in the “Instructions” section.

4.2.6 ANC Lab Reporting Form

See revised ANC Lab Reporting Form. Two minor edits in the “Hospice Care” section.

4.2.7 Guide for HCPs

See the revised Guide for HCPs. In addition to the edits and comments embedded in the Guide, the following comments are highlighted below:

- A. We note the improvement in formatting and addition of boxes and graphics.
- B. The revisions you requested to address concerns in the “how is a patient monitored if clozapine treatment is discontinued for neutropenia?” section (and related revisions in the “can a patient be rechallenged with clozapine?” section) were not incorporated. See revisions which are consistent with the FDA June 5, 2015 comments.
- C. Insert the proper dates throughout the Guide.
- D. With regard to the NNRMF, we note that the following text was omitted in June 26, 2015 version – “Patients were listed in the NNRMF if a patient had a WBC less than 2,000 or an ANC less than 1000.” We re-inserted this text. This is important context as to what the NNRMF is to readers/participants who are not familiar with the NNRMF. If this text is problematic, please explain, provide alternative text, and contact us for a teleconference.
- E. “How do I authorize continuation of clozapine when my patient’s ANC is ...” section did not read correctly. See revisions.

- F. Revise the color and text (replace (b) (4) with “Pharmacies”) for the Section 4 header to be consistent with burgundy color for pharmacies.

4.2.8 Knowledge Assessment for HCPs

See the revised Knowledge Assessment. One minor edit to correct the color of the header.

4.2.9 Guide for Patients and Caregivers

See the revised Guide. Two minor edits.

4.2.10 REMS Website

Apply all applicable comments provide in the other materials to the website. Comments on the screenshots submitted July 10, 2015 will be provided under separate cover.

4.3 REMS SUPPORTING DOCUMENT

- A. REMS Assessment Plan: Update the REMS Assessment Plan to reflect the alignment reached during the July 23, 2015 teleconference.

See revised Supporting Document.

4.3.1 Distributor Enrollment Form – no comments.

4.3.2 Prescriber Designee Educational Program

See revised Prescriber Designee Education Program. One minor edit to add clarifying language “moderate to severe”.

4.3.3 Prescriber Designee Knowledge Assessment – no comments.

4.3.4 Pharmacy Staff Attestation Language

See revised Pharmacy Staff Attestation Language. Six minor edits to use the term/concept “enroll” consisting to reduce confusion, delete misplaced text, and simplify language.

4.3.5 Transition Plan Materials - see revised materials.

Letters for Wave 1 and the “What’s New with Clozapine” continue to require substantive formatting and organization revision to improve the readability of these pieces.

Review and revise accordingly to ensure all materials include the appropriate dates. We note that pieces continue to include “<<date>>”, “Day 30”, etc. text which is meaningless to the recipients of these pieces.

See revisions and comments. If you do not agree with these revisions, contact us for a teleconference.

We note that Wave 2 and 3 have not previously been submitted. See revised materials.

- A. Pharmacy Letter Wave 1

- B. Pharmacy Letter Wave 2
- C. Pharmacy Letter Wave 3
- D. Prescriber Letter Wave 1
- E. Prescriber Letter Wave 2
- F. Prescriber Letter Wave 3
- G. Dear Professional Society – Pharmacy
- H. Dear Professional Society – Prescriber
- I. What’s New with Clozapine: An Overview

5. COMMENTS TO THE CPMG SENT JULY 31, 2015 – WEBSITE SCREENSHOTS

- Thank you for providing some written narration to understand the drop down menus and how different screen shots are related.
- We noted a few items that were identified in the Round #3 submission, not addressed in the Round #4 submission, and not identified as comments CPMG communicated about rejecting. Therefore, these issues were identified and commented upon.

Below we have provided comments that were are more global changes or repeated on multiple screenshots.

Part 1

- Based on the pdf presentation, the font size for the running footer is substantially larger than primary information (e.g., instructions and patient management information) on the screenshots. Review all screenshots to maximize readability in the online format. We recommend deleting or reducing the running footer font size and increasing the font size of the instructions and patient management text.

While we do not object to this running footer, it does not need to appear on all pages.

1. User Identification

- We recommend including instruction on this page to better direct the user to ensure that users who participated in the previous registries FIRST attempt to find their pre-populated information. We are concerned that users first assumption will be that - yes, I am a "new user" when that is likely not the case. Therefore, revise this page to better drive users to first check if their data was transferred for them.

In addition, we recommend listing “previous registry user” as the first option in the drop-down menu.

- Refer to the same comment conveyed in Round 3 Submission as follows: (b) (4) is not a word used throughout the REMS materials to describe the REMS Program.

Revise this term and the corresponding buttons. For example: "or press the NEW Clozapine REMS User button..." or "new REMS user" or "new user".

Revise to remove globally the term (b) (4) when referring to the Clozapine REMS Program.

2.4 Chain Authorized Representative Confirmation

- Please refer to our previous comments regarding this language: This statement (b) (4) misleadingly implies (b) (4) when this is not the case. The AR has completed the AR certification. (b) (4)

Revise this statement. For example: "Certification Confirmation --- Congratulations! You have successfully completed the required authorized representative certification. You can now certify your pharmacy locations."

or

"Certification Confirmation --- Congratulations! You are now certified as an authorized representative in the Clozapine REMS Program. You can now certify your Headquarters."

The second option is consistent with the Prescriber Confirmation (4.4, page 39) Round 3 screenshot submission.

Consider increasing the font size "if you are ready to certify...." in the pdf presentation, it is small and easy to overlook.

4. My Account – Confirmation pages

- Across the username, password, and email address screenshots "change confirmation" screenshots. It was unclear why the "to change your username/password/email address..." instruction and box appeared on the confirmation page. Consider deletion.

Part 2

- Based on the pdf presentation, the font size for the running footer is substantially larger than primary information (e.g., instructions and patient management information) on the screenshots. Review all screenshots to maximize readability in the online format. We recommend deleting or reducing the running footer font size and increasing the font size of the instructions and patient management text.

1.2.1 Prescriber Dashboard Patient Tab Collapsed

- For the terms circled, please note our previous comment: Explain how you will ensure that users understand the definitions of these terms.
- Revise to state - "A red flag indicates this patient is an NNRMF patient",

In addition, please note our Round 3 comments: This description is not adequate to convey to the reader what "NNRMF" is. Revise to provide more information to the user. For example, hyperlink the "NNRMF" so that a pop-up box will appear providing a short definition of NNRMF (as it appears in the HCP Guide) and include a graphic of the red flag in the text here for visual association with what appears in the dashboard.

1.2.8 and 1.3.8 Eligibility Check

Please explain the purpose of a prescriber and prescriber designee (unless the designee is also the dispensing pharmacist) needing to perform an eligibility check. Based on the purpose, revise the instructions on these screenshots.

It is not clear how the prescriber (or designee who is not the dispensing pharmacist) would know the necessary dispensing and pharmacy identification information in order to perform this eligibility check.

1.4.2 Add lab and eligibility check and 1.4.4 Add lab and predispose authorization

We note that the PDA screenshot (page 37) and the eligibility check screenshot are identical with regard to what information is collected. Explain how the website guides pharmacists in an inpatient vs outpatient pharmacy setting to understand the need to obtain a pda vs the need to perform an eligibility check. Revise accordingly.

For example:

Eligibility Check is for Inpatient Use.

Before dispensing clozapine to an inpatient, complete and submit the information below to verify patient eligibility in the Clozapine REMS Program. If you have lab information you may enter it here...."

For Outpatient Use - click here to obtain predispose authorization for the outpatient.

If the wrong verification is obtained, explained how this will impact assessment of the program.

ATTACHMENTS

- **REMS Document**
- Prescriber Enrollment Form
- Prescriber Designee Enrollment Form
- Chain Headquarters Pharmacy Enrollment Form
- Pharmacy Enrollment Form
- Patient Enrollment Form
- ANC Lab Reporting Form
- Guide for HCPs
- Knowledge Assessment for HCPs
- Guide for Patients and Caregivers
- **REMS Supporting Document**
- Distributor Enrollment Form
- Pharmacy Staff Attestation Language
- Prescriber Designee Education Program
- Prescriber Designee Knowledge Assessment
- Dear Prescriber Letters – wave 1, 2, and 3
- Dear Pharmacist Letter – wave 1, 2, and 3
- Dear Professional Society Letter – Prescriber
- Dear Professional Society Letter - Pharmacy
- What’s New with Clozapine – An Overview
- FDA Response to “Submission #3 website screenshots feedback response” slide set
- Website screenshots

215 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE C BERKMAN ROBOTOM
08/04/2015

KIMBERLY LEHRFELD
08/05/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS)

Date: June 8, 2015

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.
Health Communications Analyst
(DRISK)

Team Leader: Kim Lehrfeld, Pharm.D.
DRISK

Deputy Division Director:
(Acting) Reema Mehta, Pharm.D.
DRISK

Subject: Review of CPMG's April 17, 2015 proposed Single
Shared System REMS

Drug Name(s): Clozapine

Therapeutic Class: atypical antipsychotic

Dosage and Route: oral

Drug	Application Number	Applicant	Date Received	eCTD Sequence #/ Supporting doc
Clozaril	NDA 019758	Novartis	4/23/15	0062/456
Clozapine	ANDA 074949	Teva	4/24/15	0008/334
	ANDA 076809			0007/177
	ANDA 203039			0009/11

	ANDA 90308			0002/31
	ANDA 075417 ANDA 201824	Mylan	4/24/15	0031/129 0019/23
	ANDA 075713	Caracco/Sun	4/21/15	0009/120
	ANDA 203807	Actavis/Watson	4/22/15	0011/12
Fazaclo ODT	NDA 021590	Jazz	4/24/15	0017/328
Versacloz	NDA 203479	Jazz	4/24/15	0061/93

OSE RCM #: 2014-2345

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This is a review of the Clozapine Product Manufacturers Group (CPMG) revised proposed risk evaluation and mitigation strategy (REMS) for a single shared system REMS (SSSR) submitted via email on April 17, 2015. The same proposed SSSR was submitted in parallel to the individual NDA and ANDA applications.

A comprehensive review of the regulatory history and rationale for the design of the SSSR will be documented in a subsequent review.

2 MATERIALS REVIEWED

CPMG's proposed SSSR. Submitted via email on April 17, 2015. The submission includes the following materials:

1. REMS Document
2. REMS Supporting Document
 - o Transition Plan Materials
 - Dear HCP Letter
 - "What's New with Clozapine" Overview
 - Dear Professional Society Letter
3. Guide for HCPs
4. Overview for HCPs
5. Knowledge Assessment for HCPs
6. Guide for Patients and Caregivers
7. Chain Headquarter Pharmacy Enrollment Form
8. Prescriber Enrollment Form
9. Prescriber Designee Enrollment Form

In addition to the proposal submitted on April 17, 2015, via email CPMG submitted other REMS materials for review:

- On April 13, 2015 via email CPMG submitted "pharmacy staff attestation language" for the proposed Clozapine REMS website
- On April 24, 2015 via email CPMG submitted the following forms:
 - o ANC Lab Reporting Form
 - o Pharmacy Enrollment Form
 - o Patient Enrollment Form
- On May 8, 2015 via email CPMG submitted the Clozapine REMS Program website screen shots.

The following materials were revised and sent to CPMG via email on June 5, 2015. The revised materials are attached to this review.

- Website screen shots

Note: Comments in Section 5 "Comments For The CPMG sent June 5, 2015" of this review were sent with these revised screenshots on June 5, 2015.

The following materials were revised and sent to CPMG via email on May 29, 2015. The revised materials are attached to this review.

- REMS Assessment Plan

The following materials were revised and sent to the CPMG via email on May 22, 2015. The revised materials are attached to this review:

- 1. REMS Document**
 2. Prescriber Enrollment Form
 3. Prescriber Designee Enrollment Form
 4. Chain Headquarters Pharmacy Enrollment Form
 5. Pharmacy Enrollment Form
 6. Pharmacy staff attestation language
 7. Patient Enrollment Form
 8. ANC Lab Reporting Form
 9. Overview for HCPs
 10. Guide for HCPs
 11. Knowledge Assessment for HCPs
 12. Guide for Patients and Caregivers
- 13. REMS Supporting Document**
 14. Dear Prescriber Letter
 15. Dear Pharmacist Letter
 16. What's New with Clozapine – An Overview

Note: Comments in Section 4 “Comments For The CPMG sent May 22, 2015” of this review were sent with these materials on May 22, 2015. Comments on all the materials submitted to FDA on April 13, 17, and 24, 2015 were included with the exception of the REMS Assessment Plan.

2.1 OTHER DRISK REVIEWS

- The following review was completed for the proposed SSSR submitted on December 23, 2014.
 - Robottom S. DRISK review signed in DARRTS on June 19, 2015 by Lehrfeld K.
- The following reviews were completed for the initial proposed SSSR submitted on September 18, 2014
 - Robottom S. DRISK review signed into DARRTS on November 19, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 3, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 19, 2014 by Lehrfeld K.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Clozapine SSSR proposal be sent to the applicant. Please request that the applicant resubmit the revised REMS (i.e., REMS

Document and all REMS materials) and Supporting Document as soon as possible to facilitate further review.

4 COMMENTS FOR THE CPMG SENT MAY 22, 2015

4.1 PRESCRIBER DESIGNEE

With regard to the Prescriber Designee, we have the following comments:

- A. We align with the CPMG’s position to include a simplified training and assessment as part of the Prescriber Designee Enrollment process.

The online training slide will consist of the responsibilities and program requirements listed in the Prescriber Designee Enrollment Form (see attached). Following this training slide, the assessment will consist of the following question: “I have reviewed the requirements of the Clozapine REMS Program. Yes. No.” If the designee clicks “No” the system can re-direct the designee to the previous slide.

A parallel paper process can be accomplished by the prescriber designee completing the enrollment form (see attached). The inclusion of “By signing this form you will act on behalf of the certified prescriber (identified below) to comply with the Clozapine REMS Program requirements. I understand, ...” creates a parallel process to the online training and assessment format.

If you believe additional training is necessary beyond what is described above, it can occur outside of and separate from the Clozapine REMS and the REMS Prescriber Designee enrollment process.

- B. Append the Prescriber Designee Enrollment Form to the REMS Document and describe this component fully in the REMS Supporting Document.

4.2 BEN DESIGNATION

We do not believe the program design is aligned with labeling. The REMS program design may result in unnecessary treatment interruptions for a patient with BEN whose diagnosis is confirmed by the prescriber at the time of enrollment. We agree with the approach described during the May 21, 2015 teleconference as an interim solution. This approach requires the prescriber (b) (4) to change the treatment status for “interrupted” to “active” and auto-populates the “treatment rationale” drop-down box.

(b) (4)

We expect the program design will be corrected as soon as possible without impacting the target action date.

4.3 REMS DOCUMENT

- A. As the REMS Document is reviewed within the Agency, additional revisions have been made. We find the revisions to be clarifying and editorial in nature and not

fundamentally changing any aspect of the program or REMS Document. The edits are in track changes along with comments.

- B. Prescriber Designee: Append the Prescriber Designee Enrollment Form to the REMS Document and describe this component in the REMS Supporting Document.
- C. Implementation System: Provide your proposed percentage of pharmacies you plan to audit within one year and every two years thereafter. The REMS Document needs to reflect this agreed percentage.
- D. See revised REMS Document.

4.4 REMS MATERIALS

The FDA review process included input from two health communications analysts and three pharmacists; this included a pharmacist and HCA who were not familiar with the clozapine SSSR.

We attempted to revise the materials to illustrate formatting/spacing. However, tables, coloring, and formatting may have shifted in transition.

We find the revisions we provided to be clarifying and are not intended to fundamentally change aspects of the program. Rather, the materials were reviewed considering first the intended purpose of the piece and then revised to be as clear, constructive and as concise as possible while adequately explaining various requirements and functions. If you identify that revisions fundamentally change the program design, identify those revisions so we can further discuss.

4.4.1 Prescriber Enrollment Form

See revised Prescriber Enrollment Form.

4.4.2 Prescriber Designee Enrollment Form

See revised Prescriber Designee Enrollment Form.

4.4.3 Pharmacy Enrollment Form

Revise the Enrollment Form to delineate more clearly the out-patient and in-patient responsibilities.

Minor edits to the attestations with the exception of delineating the in-patient responsibilities. See revised Pharmacy Enrollment Form.

4.4.4 Chain Headquarters Pharmacy Enrollment Form

Minor edits. See revised Pharmacy Enrollment Form.

4.4.5 Patient Enrollment Form

Minor edits. See reviewed Form.

4.4.6 ANC Lab Reporting Form

The “Instructions for Prescribers” section did not reference the requirement to obtain a PDA for outpatient dispensing. See revised ANC Lab Reporting Form.

4.4.7 Guide for HCPs

- A. The FDA engaged in a message mapping process along with direct input from two health communications analysts and three pharmacists. Based on their expertise, we provided substantial content (plain language), formatting, and design revisions.
- B. Delete reference to the Chain Headquarter Pharmacy Enrollment Form. Given the planned direct outreach to chain pharmacies that 1) have a contract relationship directly with the switch provider, and 2) have enrolled in one or more of the legacy registries, including information about the Chain Headquarter Pharmacy Enrollment Form adds additional confusion without little utility.
- C. See the revised Guide for HCPs.

4.4.8 Overview for HCPs

See revised Overview.

4.4.9 Knowledge Assessment for HCPs

Minor edits. See revised Knowledge Assessment

4.4.10 Guide for Patients

Minor edits. See revised Guide for Patients.

4.4.11 Pharmacy Staff Attestation Language

Given the limited nature of what the pharmacy staff can do in the system and the ultimate purpose of this aspect of the program, it is more accurate to describe this (b) (4) (b) (4) an enrollment.

Considering the enrollment of the pharmacy itself and agreement to implement staff training, (b) (4)

If you have concerns, request a teleconference for further discussion.

4.4.12 REMS Website

Apply all applicable comments provide in the other materials to the website. Comments on the screenshots submitted May 8, 2015 will be provided under separate cover.

4.4.13 Transition Plan Materials

For these materials, the FDA engaged in a message mapping process along with direct input from two health communications analysts (HCAs) and three pharmacists. Based on their expertise, we provided substantial formatting and design revisions.

- A. Consistent with the Agency’s Round 1 comments, separate the letters to be specific to stakeholder (prescribers separate from pharmacists). The purpose of the letter is to act as a “notice” providing high-level information and introduce two key messages: 1) the new shared program, 2) the new treatment/monitoring recommendations. The “goal” of this letter is fit the most critical information in a readable, user-friend format on a single page.
- B. Apply the formatting and design comments from the Guide to HCPs to the transition materials to 1) improve the readability and 2) provide a consistent experience for stakeholders.
- C. Revise the Dear Professional Society Letters to be identical in content appropriate to the stakeholder group the society represents.
- D. See attached Letter for Pharmacists, Letter for Prescribers, and ‘What’s New with Clozapine: An Overview”

4.4.14 REMS Supporting Document

- A. Review the document thoroughly to provide definitions of terms.
- B. REMS Assessment Plan: The Assessment Plan is being actively discussed. Comments on the Assessment Plan will be provided under separate cover no later than May 29, 2015. If you have concerns, request a teleconference for further discussion.
- C. See revised Supporting Document.

4.4.15 Outstanding Items

- A. Prescriber Designee alignment
- B. BEN Designation – final solution
- C. Audit Plan: We understand you plan to submit the proposed Audit Plan 90 days after approval of the REMS. However, we must understand the percentage of pharmacies you propose to audit as detailed in the REMS Document.
- D. REMS Assessment – under review.
- E. Website screen shots – under review.

5. COMMENTS TO THE CPMG SENT JUNE 5, 2015

The following comments are in response to the Clozapine REMS screen shots submitted May 8, 2015 for review. In addition, we have included follow-up comments on the Guide for Healthcare Providers – How is a patient monitored if clozapine treatment is discontinued for neutropenia?

Address the comments below and review the comments embedded in the attached pdf of the screen shots. Prepare to address the comments and questions before (or during) the website demo scheduled for June 25, 2015, and incorporate these comments and revisions into the screenshots before the next submission scheduled for July 2, 2015.

5.1.GUIDE FOR HEALTHCARE PROVIDERS - *How is a patient monitored if clozapine treatment is discontinued for neutropenia?*

Please see the following edits to address the concern/confusion you raised during the June 1, 2015 teleconference. Additional text is highlighted in orange and underlined and deleted text is highlighted in orange and marked with a ~~strike through~~. Delete the bullets in the table that deal with (b) (4)

In addition, add text to refer readers to the PI under “Can a patient be rechallenged with clozapine?”.

HOW IS A PATIENT MONITORED IF CLOZAPINE TREATMENT IS DISCONTINUED FOR NEUTROPENIA?

After discontinuing clozapine, monitor ANC according to the recommendations in [Table 1](#) as shown below.

<p>Moderate Neutropenia (500 to 999/μL)*</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> • Daily until ANC \geq 1000/μL, then • Three times weekly until ANC \geq 1500/μL <p>(b) (4)</p>
<p>Severe Neutropenia (less than 500/μL)*</p>	<p>GENERAL POPULATION</p> <ul style="list-style-type: none"> • Daily until ANC \geq 1000/μL • Three times weekly until ANC \geq 1500/μL <p>(b) (4)</p> <p>BEN POPULATION</p> <ul style="list-style-type: none"> • Daily until ANC \geq 500/μL • Three times weekly until ANC \geq patients established baseline <p>(b) (4)</p>

* Confirm all initial reports of ANC less than 1500/ μ L (ANC < 1000/ μ L for BEN patients) with a repeat ANC measurement within 24 hours

(b) (4)

- Monitor ANC in any patient reporting a fever (temperature of 38.5°C or 101.3°F or greater) during the 2 weeks after discontinuation.

- Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.
- For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for General Population patients until their ANC is greater than or equal to 1500/ μ L and for Patients with BEN until their ANC is greater than or equal to 1000/ μ L or above their baseline.

Refer to Section 2.4 of the clozapine Prescribing Information for further information.

CAN A PATIENT BE RECHALLENGED WITH CLOZAPINE?

Yes. For some patients who experience, or have experienced, moderate clozapine-related neutropenia (ANC less than 1000/ μ L) or severe clozapine-related neutropenia (ANC less than 500/ μ L), the risk of serious psychiatric illness from discontinuing clozapine may be greater than the risk of rechallenge. This may be relevant for patients with severe schizophrenic illness who have no treatment option other than clozapine.

In making the decision to rechallenge a patient, consider:

- a hematology consult
- the ANC ranges defined in the full Prescribing Information
- the patient's medical and psychiatric history
- a discussion with the patient and his or her caregiver about the benefits and risks of clozapine rechallenge
- the severity and characteristics of the neutropenic episode

Refer to Section 2.5 Re-initiation of Treatment in the Clozapine Prescribing Information for more information on how to restart Clozapien in patients who have discontinued clozapine.

5.2. Website Screen Shots

General Comments

- Overall the website looked easy to navigate to find information. Below are some general and specific comments and recommendations for improvement.
- Revise the website is consistent with FDA's comments provided on May 22, 2015.

- In the next round of screen shots, provide screen shots that show the contents of the drop down menus. It is difficult to review and assess the website without being able to understand what choices/options a stakeholder has.

1.1 Home Page: pdf page 9

- There is a substantial amount of reverse text on the home page. This makes it difficult to read the screen. Reverse text is always more difficult to read and should be avoided outside of short headings. Revise the white text font size so that text it is clearer.
- Revise the three steps for prescribers and for pharmacies to be consistent/identical to the steps on the corresponding stakeholder-specific landing pages (see pdf pages 15 and 17). Or, explain why the certification steps on the home page and stakeholder-specific landing pages should be different.
- Remove the Important Safety Information (ISI) tab from the home page and relocate the ISI to the “Resources” tab/page that contains all the prescribing information for the individual clozapine products.

The ISI is currently being reviewed and will be provided under a separate cover.

- Include a “Bookmark this page” icon in upper right-hand corner of the home page, as this website will be an important place for prescribers/other stakeholders to return.
- Underline the R-E-M-S when first referring to the REMS under the question, *What is the Clozapine REMS Program?* Revise the statement as follows under the “What is the Clozapine REMS Program?” - "A Risk Evaluation and Mitigation Strategy (REMS) is a strategy...."
- Will the "What's New?" tab be available after the transition period? If so, for how long?

1.2 - 1.6 Site Guide Pages: pdf pages 10-14

- We note that there are [Prescriber] Designee and Pharmacy Staff site guide tabs under the Support tab. Explain why these tabs are not included on the home page for these audiences as well. It may not be intuitive for the prescriber designee or authorized representative to click on the appropriate tab.
- Delete or revise the following statement "The links located at the top and bottom of every page offer information for prescribers, pharmacists, and patients. Additional information about the program is also available under Resources and through the FAWs, Site Map, and Contact Us links." The links for prescriber’s pharmacists and patients do not appear on the bottom of the page.

1.4 Patient Site Guide: pdf page 12

- Explain where users will be directed once they click the **Learn More** button.

1.7 Prescriber Certification: pdf page 15

- Insert text that explains to prescribers (and pharmacists) that they do not have to complete certification in one session.

1.8 Prescriber Designee Certification: pdf page 16

- Update the text and materials according to recent alignment about Prescriber Designee training.

1.9 Pharmacy Certification: pdf page 17

- Add "by the authorized representative" to the following sentence: "Certification in the Clozapine REMS Program includes completion of the following three steps by the authorized representative."
- It is not clear from the screen shots provided where (or how) within the website (more specifically within the pharmacy tab) the following pharmacy sub-stakeholders groups navigate the website to access and complete their respective training requirements. :
 - (1) pharmacists in non-switch pharmacy training (record of their training/completion of the KA is maintained), vs
 - (2) pharmacy staff enrollment (to gain access to the website but do not need to complete the education/KA), vs
 - (3) authorized representatives of pharmacists who are want to certify a pharmacy.

The website/pharmacy tab needs to allow these sub-groups to easily navigate to the information that is relevant to them.

1.11 Pharmacy Staff Enrollment: pdf page 19

- Add text to clarify the difference between pharmacy staff enrollment, the authorized representative's enrollment, and pharmacists' education and knowledge assessment. Also refer to similar comment on pdf page 17 (above).

1.12 Patient Information: pdf page 20

- Revise to more patient friendly/plain language text, as this tab is for patients. For example, use wording consistent with the Guide for Patients and Caregivers.

- Define neutropenia on this page using plain language terms from the Guide for Patients and Caregivers.

1.13 Program Materials: pdf page 21

- Remove the Professional Societies tab with Letter to Professional Societies, as they are not needed by others outside of their original distribution.

1.16 FAQs: pdf page 24

- When drafting responses to the FAQs, we recommend the responses be consistent with content from the approved REMS materials.

3.1 Create an Account: pdf page 33

- It is not clear from the screenshots how the "create an account" page relates to the user experience in the website. It is not clear how you navigate to this page or why it is necessary for a user to create an account. Is this specific to a stakeholder group or is anyone who visits the website expected to (or allowed) to create an account? If an account is created what does that allow the user to do?
- Clarify who is allowed to and who needs to create an account (list roles).

4.1 Prescriber Certification – Prescriber Intake: pdf page 36


- At what point in the certification process does a legacy registry prescriber have access to view their "dashboard?" We note on these screens the "my dashboard" button is visible/available (as well as throughout the educational program webpages) and appears functional on many screenshots before a prescriber is fully certified. Clarify if the dashboard button is functional, what point it becomes functional, and what activities the prescriber is able to perform before a prescriber is fully certified.

We understand that prescribers with "active" patients will have access to their dashboard to manage their current/active patients before completing certification. This question is with regard to prescribers who are not part of the "grandfather" process.

5.1 Prescriber Designee Certification: pdf page 40

- Explain where designees provide information about the prescriber he/she is associated with. The screen shots do not include how this information is captured online in order to ensure that the required prescriber confirmation has been appropriately incorporated into the online experience.

5.3 Prescriber Designee Attestation: pdf page 42

- Revise the “attestations” to be consistent with the May 22, 2015 comments.
- Revise the following statement, "By checking this box, I acknowledge that I will act on behalf of a certified prescriber to comply with the Clozapine REMS Program requirements. I hereby state that all of the information I have submitted is truthful and accurate." This statement is consistent with the text on the Designee Enrollment Form sent to CPMG on May 22, 2015.
- Delete the following text at the bottom of the box of attestations: ^{(b) (4)}
." These statements are redundant with the attestations noted above them.

6.1 Pharmacy Certification – Role Selection: pdf page 44

- The descriptions for the Chain Pharmacy Headquarters and the Outpatient Pharmacy are not clear.

For Chain Pharmacy Headquarters - explain “contracted” and consider including "Outpatient" to "Chain Pharmacy Headquarters".

For Outpatient Pharmacy - Based on our understanding that the authorized representative for an outpatient pharmacy for a "chain" could be directed to complete this enrollment form in the following instances: (1) if the chain is not contracted with the switch provider (and does not want to enter into a contract) and/or (2) if the chain does not plan to use switch technology for clozapine. Therefore, the definition should state that an authorized representative of an outpatient pharmacy is not affiliated with a "corporate pharmacy chain" contracted with the switch provider **OR** does the outpatient pharmacy(ies) does not have switch capability. In addition, the description implies that this option only applies to an “individual outpatient pharmacy” when this is not the case. Revise to explain that multiple locations can be enrolled through this mechanism.

Consider re-ordering the bullets so the outpatient bullets appear together then the inpatient.

Revise the webpage to address these issues.

- The webpage does not explain what an authorized representative must do if the authorized representative represents both inpatient and outpatient pharmacies. Does the authorized representative have to enroll twice - once for each pharmacy

type or is there a mechanism to do both in single certification process? Add text to the page to address this issue.

6.2 Role Section Confirmation: pdf page 45

- Provide the pop-up boxes for chain headquarters and out-patient pharmacy. Those screenshots were not provided.

6.4 Authorized Representative Confirmation

- This statement, "... (b) (4) implies that the (b) (4) when this is not the case. (b) (4)

Revise this statement. For example: "Congratulations! You have successfully completed the required authorized representative training. You can now certify pharmacy locations."

6.5 Pharmacy Intake: pdf page 48

- What additional information, if any, appears based on the answer to this question "can your pharmacy management system adjudicate claims online? In other words, if the authorized representative selects "no" -- do the attestations for obtaining a PDA online appear?

In the screen shots provided, there are no attestations for the Item #12 on the Pharmacy Enrollment Form regarding the PDA.

Revise these screenshots to be consistent with the comments provided May 22, 2015 and include screens shots with an explanation with how the attestations related to the PDA are functionalized on the website.

6.6 Pharmacy Attestation: pdf page 49

- Does the authorized representative have to complete the attestation screen for every pharmacy location?

The attestations regarding PDA (electronic vs online) vs in-patient do not appear on the screenshot. What type of pharmacy attestation is this example for and where do those attestations reside? The do not appear on page 48 or 49 of the pdf.

- Revise the education program to be consistent with the revisions provided on May 22, 2015.
- We note the following sections of the Guide for HCPs were omitted from the online version:
 - If a patient develops a fever, how is clozapine managed?
 - How is clozapine discontinued for neutropenia?
 - How is clozapine monitored if clozapine treatment is discontinued?
 - Can a patient be rechallenged with clozapine?
 - What do I tell my patients about clozapine?
 - How do I enroll a patient?
 - What if my patient has been treated with clozapine before?
 - How do I find out if my patient was listed in the NNRMF?
 - How do I report ANC results for my patients?
 - How do I authorize continuation of clozapine when my patient's ANC is less than 1000 or less than 500?
 - What if my clozapine patient is under hospice care?

- What is a PDA?
- How do I verify the patient is authorized to receive clozapine?

For each section listed above, explain why the section is not important for the prescriber to review in the online education program. In addition, include the rationale for creating a different educational experience for stakeholders who choose to complete the training online vs on paper.

- We note that this online version of the Guide for HCPs only references "requirements for prescribers" in the overview bullets. Has the online educational program been tailored to prescribers and the pharmacy education program is different? Please explain your intent and provide a rationale if your intent is to create two educational programs specific to the stakeholder group.
- Explain if the online "education program" be accessed without creating an account first.
- Are HCPs allowed to read the HCP Guide as part of their certification process - or must they view the web-based education program in order to access the online knowledge assessment? Both options should be clearly provided for stakeholders.

Currently, the steps note that they must first read the HCP Guide itself before taking the knowledge assessment. It should also state they could complete the online education program as another option before taking the knowledge assessment.

- We recommend that the online educational program be designed to require a certain amount of time spent on each page before clicking “next”.
- Explain how long this process will take to complete the “educational program” and “knowledge assessment” and if it all has to be done in one sitting.

Revise the webpage to include the estimated time it takes for a prescriber or pharmacist to complete the educational program and knowledge assessment online. Please also include instructions of what happens if training is interrupted. Can their progress be saved?

9.1 Knowledge Assessment: pdf page 73

- Clarify if there is a time limit in between attempts to complete the knowledge assessment.

10.1 Patient Enrollment: pdf page 88

- We note on this page that the “patient” tab is “highlighted” in purple. It appears a patient can begin to enroll themselves. Please explain why it appears this is part of the “patient” tab and clarify, as necessary, that they do not have the capability to enroll themselves in the REMS Program.

11.3 Dashboard Prescribers: pdf page 94

- NNRMF: This description of NNRMF is not adequate to convey to the reader what "NNRMF" is. Revise to provide more information to the user. For example, hyperlink the "NNRMF" so that a pop-up box will appear providing a short definition of NNRMF (as it appears in the HCP Guide) and include a graphic of the red flag in the text here for visual association with what appears in the dashboard.
- “Interrupted”, “Pre-treatment”, and “Incomplete” terms: explain how users find the definitions of these terms.
- With regard to “view lab history,” explain the planned data retention of ANCs for patients. For example, how many years of data will be maintained?

The following comments are in response to the Clozapine REMS screen shots submitted May 8, 2015 for review. In addition, we have included follow-up comments on the *Guide for Healthcare Providers – How is a patient monitored if clozapine treatment is discontinued for neutropenia?*

Address the comments below and review the comments embedded in the attached pdf of the screen shots. Prepare to address the comments and questions before (or during) the website demo scheduled for June 25, 2015, and incorporate these comments and revisions into the screenshots before the next submission scheduled for July 2, 2015.

GENERAL COMMENTS

Resubmission Requirements and Instructions: Once you have received comments on the REMS document, submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and clean MS Word versions of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format and PDF. It makes review of these materials more efficient.

ATTACHMENTS

- **REMS Document**
- Prescriber Enrollment Form
- Prescriber Designee Enrollment Form
- Chain Headquarters Pharmacy Enrollment Form
- Pharmacy Enrollment Form
- Pharmacy staff attestation language
- Patient Enrollment Form
- ANC Lab Reporting Form
- Overview for HCPs
- Guide for HCPs
- Knowledge Assessment for HCPs
- Guide for Patients and Caregivers
- Website Screen Shots
- **REMS Supporting Document**
- Dear Prescriber Letter
- Dear Pharmacist Letter
- What's New with Clozapine – An Overview
- REMS Assessment Plan

222 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

SUZANNE C BERKMAN ROBOTOM
08/04/2015

KIMBERLY LEHRFELD
08/04/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) - ADDENDUM

Date: February 12, 2015

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.
Health Communications Analyst
(DRISK)

Team Leader: Kim Lehrfeld, Pharm.D.
DRISK

Deputy Division Director:
(Acting) Reema Mehta, Pharm.D.
DRISK

Subject: Review of CPMG's December 23, 2014 proposed Single Shared System REMS

Drug Name(s): Clozapine

Therapeutic Class: atypical antipsychotic

Dosage and Route: oral

Drug	Application Number	Applicant	Date Received	eCTD Sequence #/ Supporting doc
Clozaril	NDA 019758	Novartis	1/7/2015	0059/454
Clozapine	ANDA 074949,	Teva	1/9/2015	0005/331
	ANDA 076809		1/9/2015	0004/174
	ANDA 203039		1/8/2015	0008/10
	ANDA 90308		1/8/2015	0001/30

	ANDA 075417 ANDA 201824	Mylan	1/8/2015 1/8/2015	0029/127 0018/22
	ANDA 075713	Caracco/Sun	01/08/2015	0006/116
	ANDA 203807	Actavis/Watson	1/07/2015	0008/9
Fazaclo ODT	NDA 021590	Jazz	1/9/2015	0014/325
Versacloz	NDA 203479	Jazz	1/9/2015	0057/89

OSE RCM #: 2014-2345

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1 INTRODUCTION

This is a review of the Clozapine Product Manufacturers Group (CPMG) revised proposed risk evaluation and mitigation strategy (REMS) for a single shared system REMS (SSSR) submitted via email on December 23, 2014. The same proposed SSSR was submitted in parallel to the individual NDA and ANDA applications.

A comprehensive review of the regulatory history and rationale for the design of the SSSR will be documented in a subsequent review.

2 MATERIALS REVIEWED

CPMG's proposed SSSR. Submitted via email on December 23, 2014. The submission includes the following materials

- | | |
|-----------------------------------|---|
| 1. REMS Document | 10. Pharmacy Enrollment Form |
| 2. REMS Supporting Document | 11. (b) (4) |
| 3. Distributor Enrollment Form | |
| 4. Guide for HCPs | 12. Prescriber Enrollment Form |
| 5. Overview for HCPs | 13. Prescriber Designee Enrollment Form |
| 6. HCP Knowledge Assessment | |
| 7. REMS Patient Guide | 14. ANC Lab Reporting Form |
| 8. Patient Enrollment Form | 15. REMS website screenshots |
| 9. Chain Pharmacy Enrollment Form | |

The following materials were revised and sent to CPMG via email on February 11, 2015. The revised materials are attached to this review.

- REMS Supporting Document
- Distributor Enrollment Form

The following materials were revised and sent to CPMG via email on February 6, 2015. The revised materials are attached to this review.

- Guide for HCPs
- ANC Lab Reporting Form
- REMS Document

Note: Comments on the Website screenshots and the (b) (4) (b) (4) were included in this email. See Section 4 "Comments for the CPMG."

The following materials were revised and sent to the CPMG via email on February 2, 2015. The revised materials are attached to this review:

- Chain Pharmacy Enrollment Form
- Pharmacy Enrollment Form
- Overview for HCPs
- Knowledge Assessment for HCPs

The following materials were revised and sent to the CPMG via email on January 22, 2015. The revised materials are attached to this review.

- Prescriber Enrollment Form
- Prescriber Designee Enrollment Form
- Guide for Patients and Caregivers
- Patient Enrollment Form

2.1 OTHER DRISK REVIEWS

- The following reviews were completed for the initial proposed SSSR submitted on September 18, 2014
 - Robottom S. DRISK review signed into DARRTS on November 19, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 3, 2014 by Lehrfeld K.
 - Robottom S. DRISK review signed into DARRTS on December 19, 2014 by Lehrfeld K.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Clozapine SSSR proposal be sent to the applicant. Please request that the applicant resubmit the revised REMS (i.e., REMS Document and all REMS materials) and Supporting Document as soon as possible to facilitate further review.

4 COMMENTS FOR THE CPMG

The comments below were conveyed via email on February 6, 2015.

4.1 REMS DOCUMENT

As the REMS Document is reviewed within the Agency, additional revisions have been made. We find the revisions to be clarifying and editorial in nature and not fundamentally changing any aspect of the program or REMS Document.

During the review process, changes were accepted to the REMS Document.

Unfortunately, a track change document cannot be provided at this time. However, we have noted/highlighted sections where the text has changed. After you have the opportunity to review the REMS Document, please let us know what, if anything, is concerning so we can discuss.

See revised REMS Document.

4.2 REMS MATERIALS

4.2.1 ANC Reporting Form

See revised ANC Reporting Form.

4.2.3 REMS Website

Apply all applicable comments provide in the other materials to the website.

4.2.4 Outstanding Issues

The following issues are outstanding and pending agreement between the Agency and CPMG

- Transition Plan
 - Overall proposal is under review with senior management in the Agency.
 - A proposed plan for clozapine product return/pullback as part of the Transition Plan has not been presented to the Agency
 - Analysis of clozapine drug utilization by pharmacy type is ongoing with CPMG and will be presented to the Agency once completed.
- REMS Processes and Requirements
 - (b) (4)
See comments provided in Section 5.2.2.

- ‘Dosing information’ from Pharmacies

In the outpatient setting, it is our understanding that the following dosing information will be required and obtained either electronically (through the ‘switch’) or manually (via the website or verbally to the call center; ‘non-switch):

- Dispense date
- NDC
- Days’ supply
- Quantity
- Prescriber identifier

In the patient setting, what information will be obtained is not clear.

We agree obtaining a pre-dispense authorization is not necessary in the inpatient setting. We do not fully understand your proposal for inpatient use and reporting requirements and how it will ensure the REMS is able to track who is an inpatient. We understand the concern you raised with hospitals having to approve multiple forms.

Based on our understanding of the REMS and inpatient proposal, we believe it is necessary for safe use for the program to receive the following from the pharmacy: a list of inpatients who are receiving clozapine and their admit date, discharge date and acknowledgement that each patient continues to receive clozapine. We continue to believe that reporting ANC should be the primary responsibility of the prescriber.

- Treatment rationale/authorization to continue clozapine treatment.

- Website demonstration
- Distributor Enrollment

We agree that a Distributor Enrollment Form is acceptable.

- Audit Plan
- REMS Assessment Plan

- We have not started discussions regarding the content of the Assessment Plan

GENERAL COMMENTS

Resubmission Requirements and Instructions: Once you have received comments on the REMS document, submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word

Format Request: Submit your proposed REMS and other materials in MS Word format and PDF. It makes review of these materials more efficient.

ATTACHMENTS

- REMS Document
- REMS Supporting Document
- Distributor Enrollment
- Guide for HCPs
- ANC Lab Reporting Form
- Prescriber Enrollment Form
- Prescriber Designee Enrollment Form
- Guide for Patients and Caregivers
- Patient Enrollment Form
- Chain Pharmacy Enrollment Form
- Pharmacy Enrollment Form
- Overview for HCPs
- Knowledge Assessment for HCPs

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/s/

SUZANNE C BERKMAN ROBOTOM
06/17/2015

KIMBERLY LEHRFELD
06/19/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) - ADDENDUM

Date: December 18, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.
Health Communications Analyst
(DRISK)

Team Leader: Kim Lehrfeld, Pharm.D.
DRISK

Deputy Division Director:
(Acting) Reema Mehta, Pharm.D.
DRISK

Subject: Review of CPMG's September 18, 2014 proposed Single
Shared System REMS

Drug Name(s): Clozapine

Therapeutic Class: atypical antipsychotic

Dosage and Route: oral

Drug	Application Number	Applicant	Date Received	eCTD Sequence #/ Supporting doc
Clozaril	NDA 019758	Novartis	9/25/2014	0056/448
Clozapine	ANDA 074949,	Teva	9/29/2014	0002/327
	ANDA 076809		9/29/2014	0001/170
	ANDA 203039		9/26/2014	0007/9
	ANDA 90308			

			9/26/2014	28
	ANDA 075417	Mylan	9/26/2014	0027/125
	ANDA 201824		9/26/2014	0017/21
	ANDA 075713	Caracco/Sun	9/25/2014	0004/114
	ANDA 203807	Actavis/Watson	9/26/2014	0007/8
Fazaclo ODT	NDA 021590	Jazz	9/26/2014	0013/323
Versacloz	NDA 203479	Jazz	9/26/2014	0055/78

OSE RCM #: 2014-2345

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1 INTRODUCTION

This is an addendum to the DRISK review dated November 17, 2014 and signed into DARRTS on November 19, 2014 to provide comments to the Clozapine Product Manufacturers Group (CPMG) on the outstanding pieces submitted as part of the proposed risk evaluation and mitigation strategy (REMS) for a single shared system REMS (SSSR) submitted via email on September 18, 2014. The same proposed SSSR was submitted in parallel to the individual NDA and ANDA applications.

This addendum includes a revised Out-patient Pharmacy Enrollment Form, a Dear Prescriber Letter, Dear Pharmacist Letter, and “What’s New with Clozapine: An overview.”

A comprehensive review of the regulatory history and rationale for the design of the SSSR will be documented in a subsequent review.

2 MATERIALS REVIEWED

- CPMG’s proposed SSSR. Submitted via email on September 18, 2014. The submission includes the following materials
 - REMS Document
 - REMS Supporting Document
 - Dear Distributor Letter
 - Dear HCP Letter
 - Dear Professional Society Letter
 - Distributor Enrollment Form
 - Distributor Overview
 - REMS Educational Program
 - REMS HCP Guide
 - HCP Knowledge Assessment
 - HCP Overview
 - REMS ISI
 - REMS Patient Guide
 - Patient Registration Form
 - Pharmacy Attestation Form
 - Prescriber Attestation Form
 - (b) (4) Lab Reporting Form
 - REMS website screenshots

The November 19, 2014 review included comments and/or track-changes on the following materials.

- Prescriber Attestation Form
- Pharmacy Attestation Form – single-site
- Pharmacy Attestation Form – multi-site
- HCP Knowledge Assessment
- HCP Guide
- HCP Overview
- Patient Registration Form
- Patient Guide
- Website

The December 1, 2014 addendum included comments on the REMS Document, REMS Supporting Document, Distributor Letter and Overview, and Important Safety Information.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Clozapine SSSR proposal be sent to the applicant. Please request that the applicant resubmit the revised REMS (i.e., REMS Document and all REMS materials) and Supporting Document as soon as possible to facilitate further review.

4 COMMENTS FOR THE CPMG

The draft materials provided are examples of the content and organization the Agency believes is appropriate. Use these drafts as a *guide* to assist in further development of these pieces and the rest of your transition plan. We expect CPMG can improve substantially upon these materials with the collective experience, expertise, and resources available to you.

- **Transition material examples**
 - *Dear Prescriber Letter and Dear Pharmacist Letter*
 - The content of these two letters is very similar with the exception of the information pertaining to “What do I need to do?” We split the prescriber and pharmacists into two different letters in attempt to fit the information on one page and make the letters specific to the stakeholder group.
 - Overview - “*What’s new with Clozapine*”
 - This is a 3 page piece to accompany the Dear Prescriber and Dear Pharmacist letters. This piece is meant to target both prescribers and pharmacists. We considered and identified what we believe to be the most critical information to convey to these stakeholders regarding the changes to the labeling and implementation of the SSSR. While we consider this piece to be an overview, we acknowledge that there are likely more questions to cover in this piece that are critical that we did not include.
- **Outpatient Pharmacy Enrollment Form example**
 - We recommend a total of two pharmacy enrollment forms, one for Outpatient pharmacies and one for Inpatient pharmacies. An example of the Outpatient Pharmacy Enrollment is attached. We will not be drafting an Inpatient Pharmacy Enrollment Form as we believe the Outpatient form example is sufficient direction and, at present, we do not fully understand the Inpatient Pharmacy requirements to develop that form.

GENERAL COMMENTS

Resubmission Requirements and Instructions: Once you have received comments on the REMS document, submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word

Format Request: Submit your proposed REMS and other materials in MS Word format and PDF. It makes review of these materials more efficient.

ATTACHMENTS

- Dear Prescriber Letter
- Dear Pharmacist Letter
- What's New with Clozapine: An Overview
- Outpatient Pharmacy Enrollment Form

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/s/

SUZANNE C BERKMAN ROBOTOM
12/18/2014

KIMBERLY LEHRFELD
12/19/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) - ADDENDUM

Date: December 1, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Team Leader: Kim Lehrfeld, Pharm.D.
DRISK

Deputy Division Director:
(Acting) Reema Mehta, Pharm.D., M.P.H.
DRISK

Subject: Review of CPMG's September 18, 2014 proposed Single Shared System REMS

Drug Name(s): Clozapine

Therapeutic Class: atypical antipsychotic

Dosage and Route: oral

Drug	Application Number	Applicant	Date Received	eCTD Sequence #/ Supporting doc
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	ANDA 076809		9/29/2014	0001/170
	ANDA 203039		9/26/2014	0007/9
	ANDA 90308		9/26/2014	28
	ANDA 075417	Mylan	9/26/2014	0027/125

	ANDA 201824		9/26/2014	0017/21
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OSE RCM #: 2014-2345

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1 INTRODUCTION

This is an addendum to the DRISK review dated November 17, 2014 and signed into DARRTS on November 19, 2014 to provide comments to the Clozapine Product Manufacturers Group (CPMG) on the outstanding pieces submitted as part of the proposed risk evaluation and mitigation strategy (REMS) for a single shared system REMS (SSSR) submitted via email on September 18, 2014. The same proposed SSSR was submitted in parallel to the individual NDA and ANDA applications.

This addendum includes track-change version of the REMS Document and explains the status of the review of the other outstanding materials.

A comprehensive review of the regulatory history and rationale for the design of the SSSR will be documented in a subsequent review.

2 MATERIALS REVIEWED

- CPMG's proposed SSSR. Submitted via email on September 18, 2014. The submission includes the following materials
 - REMS Document
 - REMS Supporting Document
 - Dear Distributor Letter
 - Dear HCP Letter
 - Dear Professional Society Letter
 - Distributor Enrollment Form
 - Distributor Overview
 - REMS Educational Program
 - REMS HCP Guide
 - HCP Knowledge Assessment
 - HCP Overview
 - REMS ISI
 - REMS Patient Guide
 - Patient Registration Form
 - Pharmacy Attestation Form
 - Prescriber Attestation Form
 - (b) (4) Lab Reporting Form
 - REMS website screenshots

The November 19, 2014 review included comments and/or track-changes on the following materials.

- *Prescriber Attestation Form*
- *Pharmacy Attestation Form – single-site*
- *Pharmacy Attestation Form – multi-site*
- *HCP Knowledge Assessment*
- *HCP Guide*
- *HCP Overview*
- *Patient Registration Form*
- *Patient Guide*
- (b) (4) *Lab Reporting Form*
- *Website*

We stated that the REMS Document, REMS Supporting Document, letters (HCP, Professional, Distributor), Distributor Overview, and ISI are under review and will be provided under separate cover and not necessarily with this review cycle.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Clozapine SSSR proposal be sent to the applicant. Please request that the applicant resubmit the revised REMS (i.e., REMS Document and all REMS materials) and Supporting Document as soon as possible to facilitate further review *after* they have received comments on the REMS Document.

4 COMMENTS FOR THE CPMG

The table below outlines the materials CPMG has not received comments on and provides FDA response regarding the status of those comments:

Materials	FDA Comments
REMS Document	<p>The REMS Document is attached. Please note that this initial draft reflects the Agency’s most current thinking on the organization and text of the REMS Document. We are providing this document at this time to offer CPMG a more comprehensive understanding of the Agency’s thoughts on the Clozapine SSSR. Please understand that additional changes are expected as we discuss the SSSR with CPMG and it goes under additional review within the Agency.</p> <p>Given the substantial revisions, we are not providing a track-change version of the REMS Document.</p>
REMS Supporting Document	<p>Given the substantial revisions to the REMS, we are not providing a track change version of the Supporting Document until it accurately reflects the current state of the REMS. Submit a revised version with the next review cycle.</p>
Letters (DHCP, Professional)	<p>Please reference our comments regarding the Transition Plan. We do not have revisions to these pieces at this time but will provide comments as soon as possible.</p> <p>Materials that support the transition plan can be submitted separately since you will be receiving comments on them at a later date.</p>
Distributor Letter and Distributor Overview	<p>In our November 17, 2014 comments, we asked CPMG to clarify the purpose of Distributor Enrollment. We have not received a response from CPMG (understandably) about your thoughts on distributor enrollment. Please refer to the draft REMS document we provided today for further information on our current thinking about Distributor Enrollment. Once we receive a response</p>

	to our November 17 comment, we will provide further information comment on any pieces related to distributors until after that response is received.
Important Safety Information	As explained in the November 17, 2014 comments, the ISI will only appear on the SSSR website. We will provide comments at a later time.

Website: We provided high-level comments on the website in the November 17, 2014 comment set. Pending further understanding of the operation of the website and receipt of the website in format we can provide track-change edits, therefore we will provide additional comments on a revised version during a subsequent review cycle. We expect you to apply the comments provided on the various enrollment forms and educational materials along with these high-level comments to revise the website accordingly.

We feel that we have provided substantive comments on the major aspects of the Clozapine SSSR in order for you to meet the previous timelines.

GENERAL COMMENTS

Resubmission Requirements and Instructions: Once you have received comments on the REMS document, submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word

Format Request: Submit your proposed REMS and other materials in MS Word format and PDF. It makes review of these materials more efficient.

ATTACHMENTS

- REMS Document

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE C BERKMAN ROBOTOM
12/01/2014

KIMBERLY LEHRFELD
12/03/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS)

Date: November 17, 2014

Reviewer(s): Suzanne Robottom, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Joan Blair, R.N., M.P.H.
Health Communications Analyst
DRISK

Team Leader: Kim Lehrfeld, Pharm.D.
DRISK

Deputy Division Director:
(Acting) Reema Mehta, Pharm.D.
DRISK

Subject: Review of CPMG's September 18, 2014 proposed Single
Shared System REMS

Drug Name(s): Clozapine

Therapeutic Class: atypical antipsychotic

Dosage and Route: oral

Drug	Application Number	Applicant	Date Received	eCTD Sequence #/ Supporting doc
Clozaril	NDA 019758	Novartis	9/25/2014	0056/448
Clozapine	ANDA 074949,	Teva	9/29/2014	0002/327
	ANDA 076809		9/29/2014	0001/170
	ANDA 203039		9/26/2014	0007/9
	ANDA 90308		9/26/2014	28

	ANDA 075417	Mylan	9/26/2014	0027/125
	ANDA 201824		9/26/2014	0017/21
	ANDA 075713	Caracco/Sun	9/25/2014	0004/114
	ANDA 203807	Actavis/Watson	9/26/2014	0007/8
Fazaclo ODT	NDA 021590	Jazz	9/26/2014	0013/323
Versacloz	NDA 203479	Jazz	9/26/2014	0055/78

OSE RCM #: 2014-2345

*** This document contains proprietary and confidential information that should not be released to the public. ***

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1 INTRODUCTION

This is a review of the Clozapine Product Manufacturers Group (CPMG) proposed risk evaluation and mitigation strategy (REMS) for a single shared system REMS (SSSR) submitted via email on September 18, 2014. The same proposed SSSR was submitted in parallel to the individual NDA and ANDA applications.

Clozapine, the first atypical antipsychotic, was approved in 1989. It is available in the US as an oral tablet (Clozaril and generic), and orally disintegrating tablet (Fazaclo and authorized generic) and an oral suspension (Versacloz).

Because of the risk of severe neutropenia, at the time of initial US approval, Clozaril was approved with a restricted distribution program. As clozapine ANDAs and new formulations (NDAs; Fazaclo and Versacloz) were approved, each manufacturer developed a separate but comparable restricted distribution program for their product(s). On March 27, 2008, the Food and Drug Administration Amendments Act (FDAAA) took effect providing FDA the authority to require programs, coined REMS, to ensure that the benefits of the drug outweighed the risks. Clozapine was included on the list of products deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of FDAAA. The sponsors of such listed products were required to submit a REMS proposal on September 16, 2008.

As part of the “deemed REMS” review process, FDA determined a SSSR was necessary to encompass all clozapine products due to concerns over safety and burden with having several separate programs. In addition, FDA determined that clozapine labeling with regard to the risk of neutropenia was outdated and must be revised.¹ The SSSR and labeling negotiations have occurred in parallel.

A comprehensive review of the regulatory history and rationale for the design of the SSSR will be documented in a subsequent review.

2 MATERIALS REVIEWED

- CPMG’s proposed SSSR. Submitted via email on September 18, 2014. The submission includes the following materials
 - REMS Document
 - REMS Supporting Document
 - Dear Distributor Letter
 - Dear HCP Letter
 - Dear Professional Society Letter
 - Distributor Enrollment Form
 - Distributor Overview
 - REMS Educational Program
 - REMS HCP Guide
 - HCP Knowledge Assessment
 - HCP Overview
 - REMS ISI
 - REMS Patient Guide
 - Patient Registration Form

- Pharmacy Attestation Form
- Prescriber Attestation Form
- (b) (4) Lab Reporting Form
- REMS website screenshots

The REMS Document, REMS Supporting Document, letters (HCP, Professional, Distributor), Distributor Overview, and ISI are under review and will be provided under separate cover.

- CPMG information request response to DRISK October 10, 2014 information request. Signed in DARRTS on October 22, 2014 by Flowers L.

DRISK requested CPMG describe and clarify the proposed patient enrollment process and definition of terms in order to review adequately the proposed patient Enrollment Form.

3 SUMMARY OF CPMG’S PROPOSED REMS

CPMG submitted a proposed SSSR that includes prescriber certification, pharmacy certification, patient registration, documentation of safe use conditions, and a patient registry. CPMG included an implementation system and proposed to submit assessment annually from the date of REMS approval.

- *Reviewer Comment: The CPMG-proposed REMS (b) (4) DRISK has identified several problems (b) (4) These concerns were communicated to CPMG in a teleconference on October 23, 2014 and discussions are ongoing. These concerns will be described in a subsequent review.*

With regard to the REMS educational materials, these proposed materials are text heavy, lengthy, lack focused messaging, and omit important information. The proposed plan to outreach to stakeholders to communicate the SSSR and the labeling changes appears to consist of three letters (Professional Society, HCP, and Distributor, respectively).

- *Reviewer Comment: DRISK directed two “message mapping” sessions with the Division of Psychiatry Products to identify the key messages and sub-messages to better focus the educational materials. The educational materials are revised based on the key messages identified.*

A multi-faceted approach leveraging individual-targeted (letters, sales representative interactions, meeting booths) efforts and mass communication (professional societies, journal advertisements, internet) efforts is necessary to facilitate the transition from the individual registries to the SSSR, to ensure prescribers and pharmacists are aware of the new treatment and monitoring recommendations, and the need to be certified in the SSSR to continue to prescribe or dispense clozapine.

¹ For information regarding the labeling revisions, refer to Duncan LE. Labeling review. Signed in DARRTS on August 15, 2014 by Duncan LE.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Clozapine SSSR proposal be sent to the applicant. Please request that the applicant resubmit the revised REMS (i.e., REMS Document and all REMS materials) and Supporting Document as soon as possible to facilitate further review *after* they have received comments on the REMS Document.

5 COMMENTS FOR THE CPMG

5.1 REMS DOCUMENT

- A. The revised REMS document will be provided under separate cover.
- B. The Agency is considering how wholesaler/distributors are best handled in the context of REMS with ETASU. Explain why distributor enrollment through a distributor enrollment form through the REMS is necessary versus handling the requirements of the distributor through individual contractual agreements. Comments on the Distributor Letter and Distributor Overview are pending further Agency understanding of this program aspect.

5.2 REMS MATERIALS

We substantially revised the content of your materials to focus the messages on the risk addressed in the REMS (neutropenia) and how the REMS will function.

- A. Explain any pre-testing CPMG completed on the proposed materials to help us better understand the format and content of the materials. In your response, include if you plan to test the materials revised materials.
- B. The content of the revised materials is consistent with the FDA-revised labeling provided to CPMG on November 10, 2014. We recognize that labeling continues to evolve and the materials will be updated to be consistent with final labeling.
- C. Delete the footnote (b) (4) from all your materials.

5.2.1 Prescriber (b) (4)

- A. Revise the title to “Prescriber Enrollment Form.”
- B. It is not clear why NPI and DEA numbers are needed. We recommend deleting DEA and maintaining NPI. If you disagree, please explain.
- C. Please see the revised “Prescriber Enrollment Form.”

5.2.2 Pharmacy (b) (4)

- A. Revise the title to “Pharmacy Enrollment Form”
- B. We recommend creating two pharmacy enrollment forms, one for single pharmacy location to enroll (i.e., “Single Site Pharmacy Enrollment Form”) and a separate enrollment form pharmacies with multiple locations “(i.e., “Multi-Site Pharmacy Enrollment Form”). The Multi-Site Pharmacy Enrollment Form would support enrollment of pharmacies associated with a large organization through a

centralized process as we discussed during the October 23 and November 13, 2014 teleconferences.

- C. Please see the revised “Single Site Pharmacy Enrollment Form” and “Multi-Site Pharmacy Enrollment Form.”

5.2.3 Educational Program for HCPs and HCP Guide

- A. Merge these two educational pieces into a single, comprehensive educational piece. Revise the title of the Guide to “Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers.” This title emphasizes the focus of the Guide and the REMS.
- B. Remove all information that does not relate to the minimizing the risk of severe neutropenia or the REMS. For example, remove the (b) (4)
- C. Explain the anticipated size and presentation you propose for the final Guide. At present the material is very text heavy.
 - 1) Include graphics and color to increase the readability of the Guide.
 - 2) Because of the overall length of the piece and amount of text, revise the Guide to reduce reader fatigue. For example, widen the margins or present text in columns under each section/question heading.
 - 3) We recommend leveraging the expertise within the sponsor manufacturers and your selected vendor for recommendations to improve the look and feel of the REMS materials.
- D. The presentation (font, colors, graphics, bulleting, etc) as provided in the FDA revisions are very basic and should be considered an example.

We anticipate CPMG is able to substantially improve the overall presentation with your resources.
- E. Explain how you plan to address patients who are under the care of hospice within the REMS (operationally) and in this Guide. Refer to section 2.5.
- F. In the Guide, include information regarding any criteria for designees and how this aspect will work. Refer to section 3.1.
- G. In this Guide, briefly explain how patients who were listed in the NNRMF will be identified in the SSSR. Refer to section 3.5.
- H. Please see the revised “Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers.”

5.2.4 Overview for Healthcare Professionals

- A. Please see the revised Overview.

5.2.5 HCP Knowledge Assessment

- A. We agree with requiring the same knowledge assessment for both prescribers and pharmacists.
- B. Remove questions that do not relate to assessing knowledge/awareness regarding the risk of severe neutropenia and the safe use practices required by the REMS.
- C. Please see the revised “Knowledge Assessment for Healthcare Providers.”

5.2.6 Important Safety Information (ISI)

- A. The ISI is not part of the REMS and will not be included with any of the REMS materials except for the website. The REMS website will include a tab for the ISI as you have proposed. Any comments on the ISI will be provided under separate cover.

5.2.7 Patient (b) (4) Form

- A. Revise the title of this form to “Patient Enrollment Form.”
- B. Explain why (b) (4) is necessary. Is it to aid in linking an existing patient in the database to a new enrollment?

We acknowledge the importance of screening newly enrolled patients to link them to previous clozapine treatment. However, we expect that each patient is given a new unique identification number for other purposes moving forward (e.g., system alerts/system-prescriber communication, FDA reports).

- C. Add text to determine if the patient has benign ethnic neutropenia (BEN).
- D. Remove “(b) (4)” and “(b) (4).” This information does not appear necessary and may impose additional confusion. We expect every newly enrolled patient is screened to ensure duplicative files are not created and ensure appropriate monitoring is completed based on the labeling recommendations.
- E. With regard to “blood draw date” and “ANC,” providing this information should be optional at the time of enrollment. While this information is a requirement for initiating treatment, it is not a requirement to enroll the patient.
- F. Revise the (b) (4) section to indicate the prescriber (or his/her designee(s)) is responsible for enrolling the patient.
- G. Please see the revised “Patient Enrollment Form.”

5.2.8 (b) (4) Patients and Caregivers

- A. Revise the title to “What You Need to Know about Clozapine: A Guide for Patients and Caregivers.” This title emphasizes the focus of the Guide.
- B. Remove all information that does not relate to the minimizing the risk of severe neutropenia and the REMS. For example, remove (b) (4)

- C. Explain the anticipated size and presentation you propose for the final Guide. At present the material is very text heavy.
- 1) Include graphics and color to increase the readability of the Guide.
 - 2) Because of the overall length of the piece and amount of text, revise the Guide to reduce reader fatigue. For example, widen the margins or present text in columns under each section/question heading.
 - 3) We recommend leveraging the expertise within the sponsor manufacturers and your selected vendor for recommendations to improve the look and feel of the REMS Materials.
- D. The presentation (font, colors, graphics, bulleting, etc) as provided in the FDA revisions are very basic and should be considered an example.

We anticipate CPMG is able to substantially improve the overall presentation with your resources.

We must approve the materials in their final format.

5.2.9 (b) (4) ANC Lab Reporting Form

- A. Remove this form. ANC results will be reported directly to the website or by phone.

5.2.10 Website

- A. The 16 screenshots provided to date reflect static pages for prescribers and pharmacies. Identify when you will be submitting the website in totality, including the patient enrollment and management aspects of the website for review. We plan to schedule a teleconference for CPMG to demonstrate how the website will function and operate on all program aspects (e.g., view the education, complete the knowledge assessment, enroll, and manage patients).
- B. Apply all applicable comments provided in the above materials to the website.
- C. Provide a link to Prescribing Information on the home page, which takes you to a list of all clozapine products, like the ER/LA REMS program here:
<http://www.er-la-opioidrems.com/IwgUI/rems/products.action>
- D. Delete (b) (4), as it makes it more difficult to find the other REMS resources and materials (b) (4)
- E. Add the Clozapine REMS Patient Guide to the list of materials under the Prescriber Certification and Pharmacy Certification tabs, so they know this is available for patient counselling sessions. It should also remain under the patient tab.
- F. Under the patient tab, the text should only mention the serious risk of neutropenia re: why a REMS is in place to address just this risk, like the title of the patient

brochure indicates: "What You Need to Know About Clozapine and Neutropenia: A Guide for Patients and Caregivers."

- G. Clarify the differences in what webpage pulls up when you click on "[REDACTED] (b) (4)" on the home page vs. "Learn More" and "Begin Now" on the site guide pages for prescribers and pharmacies. Could these tabs be relabeled for clarity or consistency?

5.2.11 Transition Plan

Your transition plan to outreach to various stakeholders regarding the SSSR and labeling changes appears to consist of three letters (HCP, Professional Society, and Distributor). A multi-faceted approach is necessary to communicate these major changes to ensure prescribers and pharmacists are aware of the new treatment and monitoring recommendations and the need to be certified in the SSSR to continue to prescribe or dispense clozapine.

Comments on the proposed letters will be provided under separate cover.

The Transition Plan should include but not limited to the following:

A. Dear HCP Letters (print and email)

- Send this letter X weeks after the REMS is approved to those currently enrolled in the existing registries and those who might be interested in prescribing clozapine for the first time (due to expanded availability and monitoring guidelines).
- Envelope states, "New Clozapine Safety Information Required by FDA."
- Email subject line states, "New Clozapine Safety Information Required by FDA."
- Include the Clozapine SSSR HCP Overview and the Clozapine "What's New"/Transition Guide (described below) with these Dear HCP letters.
- Send this letter and/or additional reminders (e.g., phone calls, emails, etc.) again XX times at XX months after initial letter to remind those who have not yet enrolled and who have been in existing registries to enroll - especially if they have active patients. Prescribers must be adequately reminded to enroll before the existing registries close to minimize continuity of care issues.
- Clearly state that "If you plan to continue prescribing clozapine, you must enroll in the Clozapine REMS Program by DATE."
- Explain the scope of reach for these letters along with the timing and frequency.

B. Dear Professional Society Letters to ASH (print and email)

Send a letter to American Society of Hematology informing their members of the ANC monitoring guidelines and possible consults from clozapine prescribers.

C. Dear Professional Society Letters (print and email)

- Send this letter within the first month after the REMS is approved and again one month before the current registries are closed.
- Envelope would state "New Clozapine Information Required by FDA."
- Email subject line would state "New Clozapine Information Required by FDA."
- Include Clozapine SSSR HCP Overview Guide and Clozapine "What's New"/Transition Guide (described below) with the Dear Professional Society letters to members of the following professional societies at minimum:
 - American Psychiatric Association
 - American College of Psychiatrists
 - American Association for Geriatric Psychiatry
 - American Association of Chairs of Departments of Psychiatry
 - American Association of Directors of Psychiatric Residency Training
 - American Board of Psychiatry and Neurology
 - American College of Neuropsychopharmacology
 - American Pharmacists Association
 - American Society of Health System Pharmacists
 - National Association of Chain Drug Stores
 - American College of Clinical Pharmacy

D. Clozapine "What's New" Transition Guide

- Create a short, overview piece explaining what is new with clozapine and the combining the individual registries into a single REMS program.
 - Show comparative information (chart) about old clozapine registries and the new Clozapine REMS Program
 - List bulleted content on the cover of the guide
 - Clearly indicate "NEW!" on cover
- Send out with Dear HCP Letters and Dear PS Letters, distributed during sales calls, and make available at scientific meetings.

E. Journal Advertisement

- Create an advertisement to provide a summary of Clozapine REMS Program and content from the Clozapine "What's New" Transition Guide
 - Show comparative information (chart; described above) about old clozapine registries and new Clozapine REMS Program (*IF* not too lengthy or complex)
 - Include important dates for enrollment
- The advertisement should recur with XX frequency throughout the duration of the transition period to remind prescribers and pharmacists of the changes and to enroll.
- Propose a list of journals. Consider the following professional psychiatry and pharmacy journals:
 - American Psychiatric Association
 - American College of Psychiatrists

- American Association for Geriatric Psychiatry
- American Association of Chairs of Departments of Psychiatry
- American Association of Directors of Psychiatric Residency Training
- American Board of Psychiatry and Neurology
- American College of Neuropsychopharmacology
- Archives of General Psychiatry
- Journal of Clinical Psychiatry

F. Banner Advertisement on Professional Society Websites

Create a banner advertisement for placement on professional society websites to communicate the new SSSR and link to the Clozapine SSSR program website.

G. Pop-up ad on individual existing Clozapine Registry websites

Create a prominent promotion/pop up ad or link to Clozapine REMS on all individual registry websites requiring prescribers to click it to remove it and include a link to the SSSR website and where to find more information. This should appear throughout the duration of the transition period.

H. Pop-up ad on Clozapine SSSR Program website

Create a “what’s new” pop-up ad for the SSSR website that would link to the Transition Guide. The pop-up should appear for the duration of the transition period.

I. Link to REMS on individual product websites

Include a prominent link to the new Clozapine SSSR program website on each individual product websites.

J. Pop-up ad on individual product websites

Consider creating a pop-up ad to appear on the individual clozapine product websites. In the pop-up, include a link to the SSSR website and where to find more information. This should appear throughout the duration of the transition period.

K. Scientific Meetings

Prominently display and provide the Transition Guide, Clozapine SSSR HCP Overview, and the Prescribing Information at any scientific meetings in which any of the clozapine sponsors plan to have a presence (e.g., a booth) during the transition period.

L. Power Point Slides

Create a short set of slides (3-7 slides) describing the new Clozapine REMS Program with content from the Transition Guide to be used for sales calls during transition period. The Clozapine SSSR HCP Overview and Transition Guide should be made available for distribution through sales representatives if the manufacturer has a sales force for their clozapine product.

5.3 REMS SUPPORTING DOCUMENT

- A. Revise the Supporting Document to be consistent with the REMS Document and materials. Comments and revisions will be provided in the next review cycle.
- B. Information Needed for Assessment
 - 1) Comments on the Assessment will be discussed as the review of the SSSR progresses.
 - 2) Verify that CPMG intends to submit REMS Assessments as a single, joint assessment inclusive of all clozapine products and manufacturers. This approach is consistent with approved SSSRs.

5.4 GENERAL COMMENTS

Resubmission Requirements and Instructions: Once you have received comments on the REMS document, submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word

Format Request: Submit your proposed REMS and other materials in MS Word format and PDF. It makes review of these materials more efficient.

ATTACHMENTS

- Prescriber Attestation Form
- Pharmacy Attestation Form – single-site
- Pharmacy Attestation Form – multi-site
- HCP Knowledge Assessment
- HCP Guide
- HCP Overview
- Patient Registration Form
- Patient Guide

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE C BERKMAN ROBOTOM
11/17/2014

KIMBERLY LEHRFELD
11/19/2014

70 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

019758Orig1s061

ADMINISTRATIVE AND CORRESPONDENCE
DOCUMENTS

From: (b) (4)
To: Ayalasomayajula, Vasantha
Cc: J.Gross@hlstherapeutics.com; Flowers, Louis; Jenkins, Darrell; Harrison, Terry
Subject: RE: Clozapine - Materials to send BACK to CPMG
Date: Tuesday, September 08, 2015 1:26:40 PM
Attachments: [emfalert.txt](#)

Hi Vasantha,

Thank you for your confirmation regarding the Chain Headquarters and Pharmacy Enrollment Form.

Best,

(b) (4)

From: Ayalasomayajula, Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Tuesday, September 08, 2015 9:49 AM
To: (b) (4)
Cc: JGross, HLS <J.Gross@hlstherapeutics.com>; Flowers, Louis <Louis.Flowers@fda.hhs.gov>; Jenkins, Darrell <Darrell.Jenkins@fda.hhs.gov>; Harrison, Terry <Terry.Harrison@fda.hhs.gov>
Subject: RE: Clozapine - Materials to send BACK to CPMG

(b) (4)

Revision to the Chain Headquarters and Pharmacy Enrollment Form are acceptable.

Thanks,
Vasantha

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

From: Ayalasomayajula, Vasantha
Sent: Monday, September 07, 2015 9:00 PM
To: (b) (4)
Cc: 'JGross, HLS'; Flowers, Louis; Jenkins, Darrell; Harrison, Terry
Subject: FW: Clozapine - Materials to send BACK to CPMG

(b) (4)

Please see attached the following with minor edits.

- Dear Prescriber wave 1
- KA for HCPs

No additional edits to the Guide for HCPs.

DRISK is working to obtain concurrence on Chain Headquarters and Pharmacy Enrollment Form.

Thank you,
Vasantha

From: Ayalasomayajula, Vasantha
Sent: Friday, September 04, 2015 6:26 AM
To: Robottom, Suzanne Berkman; Lehrfeld, Kimberly; Mehta, Reema
Subject: FW: Clozapine - Materials to send to CPMG

From: (b) (4)
Sent: Thursday, September 03, 2015 11:31 PM
To: Ayalasomayajula, Vasantha
Cc: Jenkins, Darrell; J.Gross@hlstherapeutics.com; Harrison, Terry; Flowers, Louis
Subject: RE: Clozapine - Materials to send to CPMG

Hi Vasantha,

Per the agency's 9/1 message to CPMG, CPMG would like to respond in writing indicated that we consider the following documents final (either because FDA had no further comments per the 9/1 message or because CPMG is accepting/addressing all of FDA's edits):

- 1. Prescriber Enrollment Form
- 2. Prescriber Designee Enrollment Form
- 5. Distributor Enrollment Form
- 6. Prescriber Letter – wave 2
- 7. Prescriber Letter – wave 3
- 8. Pharmacy Letter – wave 3
- 9. REMS Document
- 10. Patient Enrollment Form
- 11. ANC Lab Reporting Form
- 13. Designee Knowledge Assessment
- 14. Designee Education
- 15. Pharmacy Staff Attestation
- 16. Guide for Patients and Caregivers
- 18. Pharmacy Letter – wave 1
- 19. Pharmacy Letter – wave 2
- 20. Professional Society – Pharmacy

- 21. Professional Society – Prescriber
- 22. What’s New with Clozapine

CPMG would like to resubmit the following revised items per FDA’s request for CPMG to resubmit updated versions prior to the 9/8 submission:

- 12. HCP Knowledge Assessment (attached in PDF and Word formats)
- 17. Prescriber Letter – wave 1
 - CPMG corrected phrasing error in “What do I need to do?” section

Additionally, CPMG noted in an 8/28 communication to FDA (accompanying message 1 of the sub. 5 screenshots) that an additional update to the below materials was required—that is, removal of (b) (4) CPMG’s reasoning is reiterated at the bottom of this email for reference. Since the versions FDA indicated as final on 9/1 did not reflect the edit, CPMG would like to resubmit the following forms:

- 3. Chain Headquarters Pharmacy Enrollment Form
- 4. Pharmacy Enrollment Form

Also per FDA’s request, CPMG has reviewed and addressed FDA’s edits to the HCP Guide. The updated HCP Guide is attached here in Word and PDF formats.

Finally, assuming that FDA approves the REMS on 9/14 as previously anticipated, CPMG respectfully requests that FDA indicate when they plan on making the approval announcement (e.g., on 9/14 before EOD), given that CPMG and their registry/call center vendor (b) (4) will need to switch phone systems on once the announcement is made.

Kind regards,
(b) (4)

Sent to FDA 8/28: Update Re: Chain Headquarters Pharmacy Enrollment Form and the Pharmacy Enrollment Form

- CPMG would also like to note that, as part of our work on the most recent iteration of the screenshot documents, we have discovered a slight discrepancy between the website and paper enrollment forms for the pharmacies.
- In the paper version of the Chain Headquarters Pharmacy Enrollment Form and the Pharmacy Enrollment Form, in the Credentials section of Authorized Representative Information, (b) (4)
- In our experience (b) (4) add burden to the program while providing little or no value. By their nature, they do not support any kind of systematic reporting. (b) (4). Also, they create the potential for additional call center work (b) (4).
- CPMG plans to (b) (4) in the paper version of the Chain Headquarters Pharmacy Enrollment Form and the Pharmacy Enrollment Form to align with

the online process. This change will be made when we make our final submission on September 8th. We wanted to communicate this to you ahead of time so there were no surprises in the final submission prior to approval on September 14th.

From: Flowers, Louis [<mailto:Louis.Flowers@fda.hhs.gov>]

Sent: Tuesday, September 01, 2015 12:38 PM

To: (b) (4)

Cc: Jenkins, Darrell <Darrell.Jenkins@fda.hhs.gov>; Ayalasomayajula, Vasantha <Vasantha.Ayalasomayajula@fda.hhs.gov>; JGross, HLS (J.Gross@hlstherapeutics.com) <J.Gross@hlstherapeutics.com>; Harrison, Terry <Terry.Harrison@fda.hhs.gov>; Flowers, Louis <Louis.Flowers@fda.hhs.gov>

Subject: Clozapine - Materials to send to CPMG

Hi (b) (4)

Please see the attached materials for the CPMG.

The following materials we have no comments/revisions and consider them final:

1. Prescriber Enrollment Form
2. Prescriber Designee Enrollment Form
3. Chain Headquarters Pharmacy Enrollment Form
4. Pharmacy Enrollment Form
5. Distributor Enrollment Form
6. Prescriber Letter – wave 2
7. Prescriber Letter – wave 3
8. Pharmacy Letter – wave 3

The final materials we have minor comments/edits and consider them final if all the revisions are addressed:

9. REMS Document
10. Patient Enrollment Form
11. ANC Lab Reporting Form
12. HCP Knowledge Assessment
13. Designee Knowledge Assessment
14. Designee Education
15. Pharmacy Staff Attestation
16. Guide for Patients and Caregivers
17. Prescriber Letter – wave 1
18. Pharmacy Letter – wave 1
19. Pharmacy Letter – wave 2
20. Professional Society – Pharmacy
21. Professional Society – Prescriber
22. What's New with Clozapine

- Comments on the Guide for HCPs and REMS Supporting Document will be provided under separate cover.
- For each piece listed above, please respond in writing if you accept the FDA edits. If you do not accept the revisions, resubmit the revised piece (via email) for review. In addition, via email only, please resubmit the following revised pieces for review as soon as possible (and in advance of 9/8 final submission):
 - HCP Knowledge Assessment
 - What’s New with Clozapine
- In addition, before the final 9/8 submission, in a separate Word document, submit (via email) a “List of Applicants.” Include the following information - manufacturer name, NDA/ANDA number, and product name. Please submit the “list of applicants” document at your earliest convenience for FDA to review.
- The website screenshots (submitted 8/28) are under review and comments will be provided under separate cover.
- Comments on the Outstanding Issues (Follow-Up to 8/20 teleconference) will be addressed under separate cover.

Final Resubmission Requirements and Instructions: For the final 9/8 submission, provide a separate, clean MS Word version of each document, form, or material, including the “List of Applicants” requested above. If you are not able to provide a particular document, form, or material in Word, submit it only as a PDF. Do not submit redlined versions of any of the materials, submit only the clean, final version.

In addition, provide the following in a single, combined PDF:

1. **REMS Document**
2. Prescriber Enrollment Form
3. Prescriber Designee Enrollment Form
4. Chain Headquarters Pharmacy Enrollment Form
5. Pharmacy Enrollment Form
6. Patient Enrollment Form
7. ANC Lab Reporting Form
8. Guide for HCPs
9. Knowledge Assessment for HCPs
10. Guide for Patients and Caregivers

In a separate PDF from the above listed materials, provide the following in a single, combined PDF:

11. **REMS Supporting Document**
12. Distributor Enrollment Form
13. Pharmacy Staff Attestation Language

14. Prescriber Designee Education Program
15. Prescriber Designee Knowledge Assessment
16. Dear Prescriber Letters – wave 1
17. Dear Prescriber Letters – wave 2
18. Dear Prescriber Letters – wave 3
19. Dear Pharmacist Letter – wave 1
20. Dear Pharmacist Letter – wave 2
21. Dear Pharmacist Letter – wave 3
22. Dear Professional Society Letter – Prescriber
23. Dear Professional Society Letter - Pharmacy
24. What’s New with Clozapine – An Overview
25. Website – transition screenshots

Please note the website is not fully accounted for in the above instructions. FDA will provide further guidance on how to append the website under separate cover.

Thank you,
Louis Flowers

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VASANTHA S AYALASOMAYAJULA
09/09/2015

Flowers, Louis

From: Flowers, Louis
Sent: Tuesday, September 01, 2015 3:38 PM
To: (b) (4)
Cc: Jenkins, Darrell; Ayalasomayajula, Vasantha; JGross, HLS (J.Gross@hlstherapeutics.com); Harrison, Terry; Flowers, Louis
Subject: Clozapine - Materials to send to CPMG
Attachments: Clozapine Proposed REMS Document_v1_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_ANC_Lab_Reporting_FINAL_v5_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Dear_Pharmacy_Letter_Wave1_v5_FINAL_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Dear_Pharmacy_Letter_wave2_v6_FINAL_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Dear_Pharmacy_Letter_wave3_v5_FINAL_2015_08_15_fda_8.25.15_noedits.pdf; Clozapine_REMS_Dear_Prescriber_Letter_Wave1_v5_FINAL_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Dear_Prescriber_Letter_Wave2_v4_FINAL_2015_08_14_fda_8.25.15_noedits.pdf; Clozapine_REMS_Dear_Prescriber_Letter_Wave3_v4_FINAL_2015_08_14_fda_8.25.15_noedits.pdf; Clozapine_REMS_Dear_Prof_Soc_Pharm_Ltr_Wave1_v5_FINAL_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Dear_Prof_Soc_Presc_Ltr_Wave1_v5_FINAL_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Distributor_Enrollment_Form_FINAL_v5_2015_08_14_fda_8.25.15_noedits.pdf; Clozapine_REMS_HCP_Knowledge_Assessment_v5_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_HQ_Chain_Pharm_Enrollment_Form_v5_FINAL_2015_08_14_fda_8.25.15_noedits.pdf; Clozapine_REMS_Patient_Enrollment_Form_FINAL_v5_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Patient_Guide_v5_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Pharmacy_Enrollment_Form_FINAL_v5_2015_08_14_fda_8.25.15_noedits.pdf; Clozapine_REMS_Pharmacy_Staff_Attestation_FINAL_v5_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Prescriber_Designee_Education_v5_FINAL_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Prescriber_Designee_Form_FINAL_v5_2015_08_14_fda_8.25.15_noedits.pdf; Clozapine_REMS_Prescriber_Designee_Knowledge_Assessment_v5_2015_08_14_fda_8.25.15.pdf; Clozapine_REMS_Prescriber_Enrollment_Form_FINAL_v5_2015_08_14_fda_8.25.15_noedits.pdf; WhatsNEWwithClozapine_Document_v3_2015_08_14.rtf

Follow Up Flag: Follow up
Flag Status: Flagged

Hi (b) (4)

Please see the attached materials for the CPMG.

The following materials we have no comments/revisions and consider them final:

1. Prescriber Enrollment Form
2. Prescriber Designee Enrollment Form
3. Chain Headquarters Pharmacy Enrollment Form
4. Pharmacy Enrollment Form
5. Distributor Enrollment Form
6. Prescriber Letter – wave 2
7. Prescriber Letter – wave 3
8. Pharmacy Letter – wave 3

The final materials we have minor comments/edits and consider them final if all the revisions are addressed:

9. REMS Document
10. Patient Enrollment Form
11. ANC Lab Reporting Form
12. HCP Knowledge Assessment
13. Designee Knowledge Assessment
14. Designee Education
15. Pharmacy Staff Attestation
16. Guide for Patients and Caregivers
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19. Pharmacy Letter – wave 2
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- Comments on the Outstanding Issues (Follow-Up to 8/20 teleconference) will be addressed under separate cover.

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19. Dear Pharmacist Letter – wave 1
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21. Dear Pharmacist Letter – wave 3
22. Dear Professional Society Letter – Prescriber
23. Dear Professional Society Letter - Pharmacy
24. What’s New with Clozapine – An Overview
25. Website – transition screenshots

Please note the website is not fully accounted for in the above instructions. FDA will provide further guidance on how to append the website under separate cover.

Thank you,
Louis Flowers

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
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10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LOUIS R FLOWERS
09/08/2015

From: [Karimattam, Albin](#)
To: [Ayalasomayajula, Vasantha](#); [DeMartino, Jim](#)
Subject: RE: CPMG Follow-Up on AE Reporting Expectations
Date: Thursday, April 09, 2015 3:16:09 PM
Attachments: [CPMG Response on AE Reporting Expectations \(04.09.2015\).docx](#)

Dear Vasantha,

Please see the attachment for CPMG's comments on FDA's response (received 4/6) regarding the AE reporting expectations. CPMG believes that we are in alignment with FDA and has no further questions at this time. Thank you again for helping to steward this process.

Best Regards,
Albin

Albin Karimattam, PharmD, JD
Asc Dir, US Safety Risk Management
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
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From: Ayalasomayajula, Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Monday, April 06, 2015 11:40 AM
To: Karimattam, Albin; DeMartino, Jim
Subject: FW: CPMG Follow-Up on AE Reporting Expectations

Albin/Jim,

I believe Susan is out of office. Please see FDA's responses to AE reporting expectations.

Thanks,
Vasantha

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)

Email: Vasantha.ayalasangamajula@fda.hhs.gov

From: Ayalasangamajula, Vasantha
Sent: Monday, April 06, 2015 11:31 AM
To: 'Kummerer, Susan'
Cc: Harrison, Terry; Jenkins, Darrell; Flowers, Louis
Subject: RE: CPMG Follow-Up on AE Reporting Expectations

Dear Susan,

Please see the attachment for FDA's response to CPMG regarding the AE reporting expectations.

Thanks,

Vasantha

From: Kummerer, Susan [<mailto:susan.kummerer@novartis.com>]
Sent: Friday, March 20, 2015 4:55 PM
To: Ayalasangamajula, Vasantha
Cc: Harrison, Terry; Jenkins, Darrell; Flowers, Louis
Subject: FW: CPMG Follow-Up on AE Reporting Expectations

Dear Vasantha,

CPMG has reviewed FDA's feedback (received on 3/9/15) on CPMG's questions regarding AE reporting expectations (originally sent 10/22/14). In response to items 1 and 3, CPMG has no further comments and thanks FDA for the information provided. In response to item 2, CPMG requests additional clarification, as presented in further detail in the attached Word document. We kindly request that FDA review CPMG's comments and provide any additional feedback as available.

Thank you for your assistance in coordinating this process, and please let me know if you have any questions or require further information.

Best regards,
Susan

CPMG

Clozapine REMS Program

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4421
10903 New Hampshire Avenue
Silver Spring, MD 20993
louis.flowers@fda.hhs.gov

Questions for FDA Regarding Adverse Event Reporting Expectations

Dear Captain Flowers,

The Clozapine Product Manufacturers Group (CPMG) has determined that further clarity is needed from the FDA relative to the reporting requirement implications from FDA's recent edits to the adverse event (AE) waiver request. As such, CPMG's Clinical Safety Subteam has prepared the following comments and questions for FDA regarding the Agency's expectations for AE reporting:

- CPMG has determined that an AE waiver is not required.
 - All events (hematologic and non-hematologic) collected by the registry are solicited.
 - Regulations and guidance documents for reporting of solicited events from post-marketing programs such as the Clozapine REMS indicate that an AE Waiver for non-serious ANC between 1000 and 1499 is not needed.

FDA response: FDA acknowledges that CPMG will consider all adverse events collected by the clozapine registry as "solicited" reports. For reporting purposes, adverse events from "solicited" sources are treated as study reports and submitted according to the requirements described in 21 CFR 314.80(e) *Postmarketing studies*. Under this regulation, CPMG applicants must submit 15-day "Alert reports" for any adverse event associated with clozapine, collected by the registry, that is both serious and unexpected and for which the applicant has determined there is a reasonable possibility that the drug caused the adverse event. CPMG applicants are not required to submit non-serious adverse events collected by the registry. You are correct that a waiver of the requirement to submit reports of non-serious, labeled AEs is not needed for cases collected by the registry.

CPMG

Clozapine REMS Program

We remind you that the reporting criteria described above are limited to adverse events collected through the registry. If a CPMG applicant receives a spontaneously reported adverse event for clozapine outside of the registry (i.e., an adverse event is reported to the sponsor), it must submit all serious and non-serious reports according to the regulations at 21 CFR 314.80.

CPMG response: CPMG agrees with Agency comments on this point. No further action required.

- Will the FDA accept aggregate reporting of ANC values by severity level from the REMS database in lieu of periodic safety reports from each sponsor?

FDA response: The aggregate information that you will provide as part of the REMS assessment report is not an acceptable substitute for the periodic safety report required under 21 CFR 314.80(c)(2) (i.e., periodic adverse drug experience reports or PADER). The periodic safety report contains information that would not be provided in the aggregate reports of ANC values. Each clozapine applicant must continue to submit a periodic safety report for its clozapine product(s).

CPMG response: For clarification, each sponsor will submit a periodic safety report, as required under 21 CFR 314.80(c)(2) (i.e., periodic adverse drug experience reports or PADER).

The question at hand is the agency's expectation that listings of non-serious ANC values would come from sponsor drug safety systems. All lab values are housed in the REMS database, not in the individual sponsor systems. Therefore, we need your approval to not submit non-serious ANC values by each sponsor in their periodic safety reports. Instead, we request that we report all ANC values in aggregate by ANC level in the REMS assessment report.

Clarification of AE Reporting Terms by CPMG (3/27/15)

In response to FDA's requests for clarification regarding two of the terms used in CPMG's 3/20 communication to FDA, please see below:

Non-Serious ANC Value—Clarification: Any ANC value greater than or equal to 1,000/ μ l that is not associated with any other adverse event where that adverse event does not meet the regulatory definition of serious

Aggregate—Clarification: All ANC values will be reported in aggregate (see example table below). If any of those ANC values are associated with an adverse event, then the value will be reported in the aggregate table and the ANC value and adverse event will be reported by the sponsor in its PADER. In addition, any ANC less than 1,000/ μ l, with or without an associated AE, will be subject to the special reporting requirement and submitted to the sponsor for expedited reporting to FDA.

FDA response 4/6/15: If adverse experience reports are collected through a registry and that information pertains to an applicant's product, it should be forwarded to the applicant so that it is part of the applicant's safety database. Therefore, any adverse experience

CPMG

Clozapine REMS Program

information associated with “non-serious ANC values” or any other ANC values obtained from the clozapine registry (and housed in the REMS database in this case) on an applicant’s product should also reside in an individual sponsor’s database.

Under the regulations, each clozapine applicant must review the information in its database (including any adverse experiences forwarded from the registry), submit reportable cases per the regulations, and include the adverse experience information from the reported cases as part of its periodic safety report.

Your proposal is that we allow each applicant to exclude listings of “non-serious ANC values” in its periodic safety report. As was described in our response to question #1, the only reportable cases from the clozapine registry are for adverse experiences that the applicant has determined to be both serious and unexpected and causally related to the use of its product. These reports are the only reports from the clozapine registry that are required to be covered in the periodic safety report. A report of a non-serious adverse experience from the clozapine registry, regardless of ANC value, is not reportable to the FDA and therefore, is not required to be part of the periodic safety report. However, the applicant must include in its periodic safety report information from any reportable, non-serious adverse experiences that were spontaneously reported to the applicant.

In regards to the table, we appreciate that you provided us an idea of what you are thinking in terms of how to present the aggregate data. While we agree with the general concepts of the table, we expect to have additional comments on the table as we continue to collaborate further on the REMS Assessment. Also, we would like to clarify in advance if the number of patients listed under each ANC category for each month will be reported as unique patient counts?

	Above 1500/ μ l		Mild Neutropenia (1000 to 1499/ μ l)		Moderate Neutropenia (500 to 999/ μ l)		Severe Neutropenia (less than 500/ μ l)		Total	
	# of labs	# of patients*	# of labs	# of patients*	# of labs	# of patients*	# of labs	# of patients*	# of labs	# of patients*
March 2015										

CPMG

Clozapine REMS Program

April 2015										
May 2015										

*Patient may appear in more than one ANC value category

[CPMG Response 4/9/15](#): The CPMG is in agreement with FDA, and for clarification the current expectation is that any PAE associated with an ANC, or not associated with an ANC, will be reported to the relevant applicants and will be subsequently be reported to FDA by applicants according to the regulations. During the REMS assessment report process, aggregate ANC values will be reported from the registry.

Also please note that aggregate patient counts may not be unique since a patient’s ANC may vary from test to test and therefore be counted in multiple “ranges” within any given reporting period.

CPMG does not believe that further action is required on this topic and thanks FDA for their previous responses.

- Expedited 15-day alert reports of both serious and non-serious outcomes for all cases of neutropenia with an ANC <1000/mm³ is not in-line with current regulations and guidance. CPMG does not object to the special reporting requirement; however, could FDA clarify why this special reporting requirement is being requested of CPMG?

FDA Response: Recent revisions to the labeling and monitoring criteria will expand the patient population receiving clozapine therapy. Given this change, FDA is requesting that applicants expedite cases of neutropenia with an ANC <1000/mm³ (i.e., submit these cases as 15-day Alert reports) that would not normally be required to be submitted because severe neutropenia is a labeled event. This would pertain to cases collected by the registry, as well as cases spontaneously reported to an individual sponsor.

We ask that each company:

1. Review, prepare, and submit the 15-day Alert reports as described under 21 CFR 314.80, which includes conducting follow-up (21 CFR 314.80(c)(1)(ii).
2. Have written procedures for identifying an adverse event report meeting the criteria (serious and non-serious outcomes for all cases of neutropenia with an ANC <1000/mm³) and submitting the 15-day Alert report to FDA.

CPMG

Clozapine REMS Program

We also ask that CPMG have a procedure for identifying a responsible sponsor when an adverse event report is received for a clozapine product and the sponsor is unknown. We want to ensure that there will be a responsible sponsor identified to conduct any necessary follow-up and submit the report to FDA.

CPMG response: CPMG agrees with Agency comments on this point. No further action required.

CPMG looks forward to receiving the FDA's feedback on the above items and appreciates FDA's time and consideration. If further clarification from CPMG is needed regarding this request, please let us know.

Best regards,
Clozapine Product Manufacturers Group (CPMG)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VASANTHA S AYALASOMAYAJULA
09/08/2015

Flowers, Louis

From: Kummerer, Susan <susan.kummerer@novartis.com>
Sent: Tuesday, August 04, 2015 5:46 PM
To: Flowers, Louis
Cc: Jenkins, Darrell; Harrison, Terry; DeMartino, Jim; Ayalasomayajula, Vasantha; Karimattam, Albin
Subject: RE: VA Participation in Shared Clozapine REMS

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Louis,

Thank you! I will share with the CPMG.

Kind Regards,
Susan

Susan Kummerer
GPRD
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7781130
Fax +1 973 7813966
susan.kummerer@novartis.com
www.novartis.com

From: Flowers, Louis [mailto:Louis.Flowers@fda.hhs.gov]
Sent: Tuesday, August 04, 2015 4:56 PM
To: Kummerer, Susan
Cc: Jenkins, Darrell; Harrison, Terry; DeMartino, Jim; Ayalasomayajula, Vasantha; Karimattam, Albin
Subject: RE: VA Participation in Shared Clozapine REMS

Dear Susan,

This email follows-up on CPMG's proposal to address VA's participation in the Clozapine REMS Program.

FDA has significant concerns with the proposed plan for VA's role in the shared Clozapine REMS Program as (b) (4). In particular, FDA is concerned that the proposal (b) (4) would not comply with the Clozapine REMS Program we plan to take action on in September. We will need time to explore internally, as well as with CPMG and VA, the implications of that proposal and possible alternatives. FDA does not wish to delay the planned action in September, so we plan to proceed under the current timeline. At a minimum, (b) (4) CPMG will be ready to receive patient data 30 days after the REMS approval date. (b) (4)

In the near future, we will

(b) (4)

Regards,
Louis Flowers

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Kummerer, Susan [<mailto:susan.kummerer@novartis.com>]
Sent: Tuesday, July 28, 2015 1:12 PM
To: Ayalasangajula, Vasantha; Karimattam, Albin
Cc: Jenkins, Darrell; Harrison, Terry; Flowers, Louis; DeMartino, Jim
Subject: RE: VA Participation in Shared Clozapine REMS

Dear Vasantha,

Thank you for the information.

Susan

Susan Kummerer
GPRD
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7781130
Fax +1 973 7813966
susan.kummerer@novartis.com
www.novartis.com

From: Ayalasangajula, Vasantha [<mailto:Vasantha.Ayalasangajula@fda.hhs.gov>]
Sent: Tuesday, July 28, 2015 12:41 PM
To: Karimattam, Albin; Kummerer, Susan
Cc: Jenkins, Darrell; Harrison, Terry; Flowers, Louis; DeMartino, Jim
Subject: RE: VA Participation in Shared Clozapine REMS

Dear Albin,

Thank you for the correspondence. The Agency continues to discuss this issue internally, our next meeting is on Wednesday and we plan to communicate with CPMG after Wednesday.

Regards,
Vasantha

From: Karimattam, Albin [<mailto:albin.karimattam@novartis.com>]
Sent: Monday, July 27, 2015 3:47 PM
To: Ayalasangmayajula, Vasantha; Kummerer, Susan
Cc: Jenkins, Darrell; Harrison, Terry; Flowers, Louis; DeMartino, Jim
Subject: VA Participation in Shared Clozapine REMS

Dear Vasantha,

Thank you for the two notes earlier today.

During last week's CPMG-FDA teleconference (7/22), FDA indicated that they expected to have an update for CPMG regarding the VA by Friday, 7/24. To our knowledge, we have not yet received such an update, and CPMG would like to take this opportunity to further emphasize a few points first shared by CPMG in a 7/13 message to FDA:

- It is understood from the July 9 conference call that the FDA will be continuing their review of the VA's ability to support the known Elements to Assure Safe Use (ETASU) in the shared Clozapine REMS Program given the output shared from discussions held to date between the CPMG and the VA Clozapine Registry team. The CPMG wanted to further provide the Agency their perspective and assumptions on impact of such discussions on the current REMS Submission approval and the anticipated shared Clozapine REMS Program phased launch timeline:

- [Redacted] (b) (4)
- [Redacted] (b) (4)
- [Redacted] (b) (4)

- If upon conclusion of FDA follow-up discussions with the VA there are changes to these assumptions noted above, the CPMG sponsors request that detailed updates be shared as soon as possible.

As we have not heard from FDA to the contrary regarding the above, CPMG is continuing to move forward per this approach. We look forward to receiving any updates from FDA regarding this topic. In the meantime, should you have any questions or comments regarding the above, please let us know.

Best Regards,
Albin

Albin Karimattam, PharmD, JD
Asc Dir, US Safety Risk Management
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

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/s/

LOUIS R FLOWERS
08/14/2015

From: Ayalasomayajula, Vasantha
To: "Kummerer, Susan"
Cc: [Jenkins, Darrell](#); [Harrison, Terry](#); [Flowers, Louis](#); [DeMartino, Jim](#); [Karimattam, Albin](#)
Subject: RE: For FDA: CPMG Follow-Up to Open Items From 7/22 TC
Date: Monday, July 27, 2015 9:23:00 AM

Dear Susan,

Please see responses in blue below.

Thanks,

Vasantha

From: Kummerer, Susan [mailto:susan.kummerer@novartis.com]
Sent: Friday, July 24, 2015 2:46 PM
To: Ayalasomayajula, Vasantha
Cc: Jenkins, Darrell; Harrison, Terry; Flowers, Louis; DeMartino, Jim; Karimattam, Albin
Subject: FW: For FDA: CPMG Follow-Up to Open Items From 7/22 TC

Dear Vasantha,

CPMG has had the opportunity to further consider FDA's comments and would like to follow up with the Agency regarding the four outstanding items from the 7/22 CPMG-FDA teleconference. Each item is listed below, along with CPMG's response. Please let us know if you have any questions. We kindly request that FDA confirm the proposed approaches are acceptable.

Best regards,
Susan

Assessment Plan – Patient Surveys

- CPMG accepts FDA's edits to the Evaluation of Knowledge/Surveys section of the RSD and has updated the RSD text as follows: "An evaluation of knowledge of patients or caregivers of the risk of severe neutropenia, and (b) (4) appropriate monitoring"

FDA Response: Thank you for the update. No further action is needed at this time.

Distributor Materials

- CPMG would like accept FDA's Option 1 to accommodate CPMG and FDA needs with respect to provision of distributor information online.
- At initial go-live of program (10/12/15) CPMG would like to include the following statement on the distributor tab:
 - For information on remaining, or becoming, a clozapine distributor, please contact the REMS Program at 844-267-8678 or contact your clozapine manufacturer directly

FDA Response: Option 1 and the proposed text is acceptable.

Updates to Online Attestations

- CPMG has elected to remove the redundant statements and maintain the "third"

statement in the online format “by checking this box...” For clarity, CPMG will strike redundant clauses on the website; we will not be changing any statements on the paper forms.

FDA Response: The proposal is acceptable.

Approach for Online Education

- CPMG has found a solution for ensuring that all HCP guide content be presented in the online education prior to go-live. CPMG is working on timing (i.e., when a screenshot version of the updated education will be available for FDA review) and will provide FDA with an update as soon as possible.

FDA Response: The proposal is acceptable.

From: Ayalasomayajula, Vasantha
To: "Karimattam, Albin"; Kummerer, Susan
Cc: Jenkins, Darrell; Harrison, Terry; Flowers, Louis; DeMartino, Jim
Subject: RE: VA Participation in Shared Clozapine REMS
Date: Tuesday, July 28, 2015 12:41:00 PM

Dear Albin,

Thank you for the correspondence. The Agency continues to discuss this issue internally, our next meeting is on Wednesday and we plan to communicate with CPMG after Wednesday.

Regards,
Vasantha

From: Karimattam, Albin [mailto:albin.karimattam@novartis.com]
Sent: Monday, July 27, 2015 3:47 PM
To: Ayalasomayajula, Vasantha; Kummerer, Susan
Cc: Jenkins, Darrell; Harrison, Terry; Flowers, Louis; DeMartino, Jim
Subject: VA Participation in Shared Clozapine REMS

Dear Vasantha,

Thank you for the two notes earlier today.

During last week's CPMG-FDA teleconference (7/22), FDA indicated that they expected to have an update for CPMG regarding the VA by Friday, 7/24. To our knowledge, we have not yet received such an update, and CPMG would like to take this opportunity to further emphasize a few points first shared by CPMG in a 7/13 message to FDA:

- It is understood from the July 9 conference call that the FDA will be continuing their review of the VA's ability to support the known Elements to Assure Safe Use (ETASU) in the shared Clozapine REMS Program given the output shared from discussions held to date between the CPMG and the VA Clozapine Registry team. The CPMG wanted to further provide the Agency their perspective and assumptions on impact of such discussions on the current REMS Submission approval and the anticipated shared Clozapine REMS Program phased launch timeline:

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

- If upon conclusion of FDA follow-up discussions with the VA there are changes to these assumptions noted above, the CPMG sponsors request that detailed updates be shared as

soon as possible.

As we have not heard from FDA to the contrary regarding the above, CPMG is continuing to move forward per this approach. We look forward to receiving any updates from FDA regarding this topic. In the meantime, should you have any questions or comments regarding the above, please let us know.

Best Regards,
Albin

Albin Karimattam, PharmD, JD
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Novartis Pharmaceuticals Corporation
One Health Plaza
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USA

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VASANTHA S AYALASOMAYAJULA
07/28/2015

From: Ayalasomayajula, Vasantha
To: [Kummerer, Susan \(susan.kummerer@novartis.com\)](mailto:susan.kummerer@novartis.com)
Cc: [Karimattam, Albin \(albin.karimattam@novartis.com\)](mailto:albin.karimattam@novartis.com); [DeMartino, Jim \(jim.demartino@novartis.com\)](mailto:jim.demartino@novartis.com); [Flowers, Louis](#); [Jenkins, Darrell](#); [Harrison, Terry](#)
Subject: FW: Clozapine REMS - Comments for CPMG
Date: Wednesday, July 22, 2015 12:12:00 PM
Attachments: [REMS Document and Materials .zip](#)
[Transition.zip](#)
[CPMG Sub 3 Website Screenshots CPMG Recommendations 2015-07-10 SBR KL edits 7.20.15.pptx](#)
[Supporting Document and Materials.zip](#)
Importance: High

Susan,

The following documents, forms, and materials are attached:

1. **REMS Document (.docx) and attachments [zip folder]**
 2. Prescriber Enrollment Form (.pdf)
 3. Prescriber Designee Enrollment Form (.pdf)
 4. Pharmacy Enrollment Form (.pdf)
 5. Chain Headquarters Pharmacy Enrollment Form (.pdf)
 6. Patient Enrollment Form (.pdf)
 7. ANC Lab Reporting Form (.pdf)
 8. Guide for HCPs (.doc)
 9. Knowledge Assessment for HCPs (.pdf)
 10. Guide for Patients and Caregivers (.pdf)

11. **REMS Supporting Document (.docx) and attachments [zip folder]**
 12. Distributor Enrollment Form (.pdf)
 13. Prescriber Designee Education Program (.pdf)
 14. Prescriber Designee Knowledge Assessment (.pdf)
 15. Pharmacy staff attestation language (.pdf)

Transition Materials [zip folder]

16. Dear Prescriber Letters – wave 1 (.rtf)
 17. Dear Prescriber Letter – wave 2 (.docx)
 18. Dear Prescriber Letter – wave 3 (.rtf)
 19. Dear Pharmacist Letter – wave 1 (.rtf)
 20. Dear Pharmacist Letter – wave 2 (.docx)
 21. Dear Pharmacist Letter – wave 3 (.docx)
 22. Dear Professional Society Letter – Pharmacy (.rtf)
 23. Dear Professional Society Letter – Prescriber (.rtf)
 24. What’s New with Clozapine – An Overview (.docx)
25. FDA Response to “Submission #3 website screenshots feedback response” slide set (.pptx)

Comments for CPMG to accompany the attached documents, forms, and materials.

1.1 REMS DOCUMENT

- A. As the REMS Document is reviewed within the Agency, additional revisions have been made. We find the revisions to be minor and editorial in nature; not fundamentally changing any aspect of the program or REMS Document. The edits are in track changes along with comments. If these edits are accepted, we believe we are in agreement with a final REMS Document.
- B. See revised REMS Document.

1.2 REMS MATERIALS

We attempted to revise the materials to illustrate formatting/spacing. However, tables, coloring, and formatting may have shifted in transition.

We find the revisions we provided to be clarifying and are not intended to fundamentally change aspects of the program. Rather, the materials were reviewed considering first the intended purpose of the piece and then revised to be as clear, constructive and as concise as possible while adequately explaining various requirements and functions. If you identify that revisions fundamentally change the program design, identify those revisions so we can further discuss.

Once the edits are accepted and the comments are addressed, we consider these materials final.

1.2.1 Prescriber Enrollment Form

See Prescriber Enrollment Form. No comments.

1.2.2 Prescriber Designee Enrollment Form

See revised Prescriber Designee Enrollment Form. One minor comment.

1.2.3 Pharmacy Enrollment Form

See revised Pharmacy Enrollment Form. Three minor edits in the "For Outpatient Only" section and "Authorized Representative Information" section.

The safe use conditions are outlined in Attestation Bullet #5, not #12. The PDA represents the verification of the safe use conditions but does not explain them. Revise the "no" option to state "as outlined in attestation #5" (not #12). If you disagree, provide your rationale and request a teleconference.

1.2.4 Chain Headquarters Pharmacy Enrollment Form

See revised Pharmacy Enrollment Form. Two minor edits in the "Authorized Representative Information" section.

1.2.5 Patient Enrollment Form

See revised Patient Enrollment Form. Three minor edits in the "Instructions" section.

1.2.6 ANC Lab Reporting Form

See revised ANC Lab Reporting Form. Two minor edits in the "Hospice Care" section.

1.2.7 Guide for HCPs

See the revised Guide for HCPs. In addition to the edits and comments embedded in the Guide, the following comments are highlighted below:

- A. We note the improvement in formatting and addition of boxes and graphics.

- B. The revisions you requested to address concerns in the “how is a patient monitored if clozapine treatment is discontinued for neutropenia?” section (and related revisions in the “can a patient be rechallenged with clozapine?” section) were not incorporated. See revisions which are consistent with the FDA June 5, 2015 comments.
- C. Insert the proper dates throughout the Guide.
- D. With regard to the NNRMF, we note that the following text was omitted in June 26, 2015 version – “Patients were listed in the NNRMF if a patient had a WBC less than 2,000 or an ANC less than 1000.” We re-inserted this text. This is important context as to what the NNRMF is to readers/participants who are not familiar with the NNRMF. If this text is problematic, please explain, provide alternative text, and contact us for a teleconference.
- E. “How do I authorize continuation of clozapine when my patient’s ANC is ...” section did not read correctly. See revisions.
- F. Revise the color and text (replace (b)(4) with “Pharmacies”) for the Section 4 header to be consistent with burgundy color for pharmacies.

1.2.8 Knowledge Assessment for HCPs

See the revised Knowledge Assessment. One minor edit to correct the color of the header.

1.2.9 Guide for Patients and Caregivers

See the revised Guide. Two minor edits.

1.2.10 REMS Website

Apply all applicable comments provide in the other materials to the website. Comments on the screenshots submitted July 10, 2015 will be provided under separate cover.

1.3 REMS SUPPORTING DOCUMENT

- A. REMS Assessment Plan: Update the REMS Assessment Plan to reflect the alignment reached during the July 23, 2015 teleconference.

See revised Supporting Document.

1.3.1 Distributor Enrollment Form – no comments.

1.3.2 Prescriber Designee Educational Program

See revised Prescriber Designee Education Program. One minor edit to add clarifying language “moderate to severe”.

1.3.3 Prescriber Designee Knowledge Assessment – no comments.

1.3.4 Pharmacy Staff Attestation Language

See revised Pharmacy Staff Attestation Language. Six minor edits to use the term/concept “enroll” consisting to reduce confusion, delete misplaced text, and simplify language.

1.3.5 Transition Plan Materials - see revised materials.

Letters for Wave 1 and the “What’s New with Clozapine” continue to require substantive formatting and organization revision to improve the readability of these pieces.

Review and revise accordingly to ensure all materials include the appropriate dates. We note that pieces continue to include “<<date>>”, “Day 30”, etc. text which is meaningless to the recipients of these pieces.

See revisions and comments. If you do not agree with these revisions, contact us for a teleconference.

We note that Wave 2 and 3 have not previously been submitted. See revised materials.

- A. Pharmacy Letter Wave 1
- B. Pharmacy Letter Wave 2
- C. Pharmacy Letter Wave 3
- D. Prescriber Letter Wave 1
- E. Prescriber Letter Wave 2
- F. Prescriber Letter Wave 3
- G. Dear Professional Society – Pharmacy
- H. Dear Professional Society – Prescriber
- I. What’s New with Clozapine: An Overview

1.4 “SUBMISSION #3 WEBSITE SCREENSHOTS FEEDBACK RESPONSE” SLIDE SET

We have reviewed the slide set titled, “Submission #3 website screenshots feedback response” submitted via email by CPMG on July 10, 2015. The FDA responses (in green text) are embedded within the attached slide set. FDA will be prepared to discuss and align on a path forward during the July 22, 2015 teleconference.

Thanks,
Vasanth

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VASANTHA S AYALASOMAYAJULA
07/28/2015

From: c Aya a ya u a, Va antha
To: c [Kunere, Susan \(kunere@va.gov \)](mailto:kunere@va.gov); [DeMartin, Jennifer \(jennifer.demartin@va.gov \)](mailto:DeMartin@va.gov)
Cc: [Jenkins, Darre](mailto:Jenkins@va.gov); [Fisher, L ui](mailto:Fisher@va.gov); Harri n, Terry
Subject: cc CPMG REMS rAe e nt Pan
Date: c Friday, May 29, 2015 3:18:00 PM
Attachments: [C_zapinerae e nt.p an29May2915.d](#)

Dear Susan,

Please see attached revisions to your assessment plan from the 17 April REMS Supporting document submission. Several proposed shell tables have been included to facilitate reporting of data. Please let us know if you would like a teleconference to discuss the assessment plan. Provide responses to the 2 comments in the document by COB on June 15, 2015.

Thanks,

***** C

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov C

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a r r s a i f a l c r i c r c r d h a w a s s i g d
l c r i c a l l y a d h i s a g i s h m a i f s a i f h l c r i c H
s i g a u r .

/s/ H

----- H

VASANT A S AYALASOMAYAJULA
06/16/2015

From: ; [Flo Loui](mailto:Flo_Loui)
To: [Kumme Susan \(u an.kumme @nova ti .com\) Ka imattam, Albin \(albin.ka imattam@nova ti .com\) D Ma tino Jim \(jim.d ma tino@nova ti .com\)](mailto:Kumme_Susan (u an.kumme @nova ti .com) Ka imattam, Albin (albin.ka imattam@nova ti .com) D Ma tino Jim (jim.d ma tino@nova ti .com))
Cc: ; J_nkin_Da_II_Ayala_omayajula_Va_antha_Ha_i_on_T_y_Sohn_Ann_J
Subject: ; FW: CPMG - Comment on c n hot
Date: Friday Jun 05 2015 5:14:19 PM
Attachments: [CPMG Web it Sc n Captu Final 2015 FDA dit comment 6.5.15.pdf](#)
[FDA R vi of Clozapin SSS REMS Web it .Jun 2015.doc](#)

Hi Susan,

Here are the comments for CPMG and the marked up website screenshots.

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Kumme Susan [[mailto: u an.kumme @nova ti .com](mailto:u an.kumme @nova ti .com)]
Sent: Thu day Jun 04 2015 1:29 PM
To: Ayala omayajula Va antha Ka imattam, Albin D Ma tino Jim
Cc: Flo Loui J_nkin_Da_II_Ha_i_on_T_y_Sohn_Ann_J
Subject: RE: jun 4-5: CPMG communication ith FDA

Dear Louis and Darrell,

The CPMG is expecting comments on the screen shots tomorrow June 5th. Do you know when we can expect them (meaning me)?

Best Regards,
Susan

Susan Kummerer
GPRD
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7781130
Fax +1 973 7813966

susan.kumme@naisc.m
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From: Ayalasomayajula Vasantha [<mailto:Vasantha.Ayalasomayajula@fda.hhs.gov>]
Sent: Wednesday June 03 2015 5:10 PM
To: Kummerer Susan; Karimattam Albin; DeMartino Jim
Cc: Flowers Louis; Jenkins Darrell
Subject: june 4-5: CPMG communication with FDA

Susan/Albin,

I will be on leave Thursday, June 4th and Friday, June 5th. Please cc Louis Flowers and Darrell Jenkins for any items that need to be sent to FDA's attention.

Thanks,

Vasantha

Sincerely,

Vasantha Ayala

Senior Regulatory Project Manager

Office of Surveillance and Epidemiology | Project Management Staff ,

Ph: 240-402-5035 (O)

Email: Vasantha.ayalasomayajula@fda.hhs.gov

FDA Review of Clozapine REMS Website

Submitted: May 8, 2015

Date: June 5, 2015

The following comments are in response to the Clozapine REMS screen shots submitted May 8, 2015 for review. In addition, we have included follow-up comments on the *Guide for Healthcare Providers – How is a patient monitored if clozapine treatment is discontinued for neutropenia?*

Address the comments below and review the comments embedded in the attached pdf of the screen shots. Prepare to address the comments and questions before (or during) the website demo scheduled for June 25, 2015, and incorporate these comments and revisions into the screenshots before the next submission scheduled for July 2, 2015.

Guide for Healthcare Providers - How is a patient monitored if clozapine treatment is discontinued for neutropenia?

Please see the following edits to address the concern/confusion you raised during the June 1, 2015 teleconference. Additional text is highlighted in orange and underlined and deleted text is highlighted in orange and marked with a ~~strike through~~. Delete the bullets in the table that deal with (b) (4) because this section is focused on how to monitor ANC when treatment is discontinued, (b) (4). In addition, add text to refer readers to the PI under “Can a patient be rechallenged with clozapine?”.

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

After **discontinuing** clozapine, monitor ANC according to the recommendations in [Table 1](#) as shown below.

Moderate Neutropenia (500 to 999/ μ L)*	GENERAL POPULATION <ul style="list-style-type: none">• Daily until ANC \geq 1000/μL, then• Three times weekly until ANC \geq 1500/μL (b) (4)
Severe Neutropenia (less than 500/ μ L)*	GENERAL POPULATION <ul style="list-style-type: none">• Daily until ANC \geq 1000/μL• Three times weekly until ANC \geq 1500/μL (b) (4)

BEN POPU ON

Daily until ANC $\geq 500/\mu$

T ree times weekly until ANC \geq patients established baseline h

(b) (4)

* Confirm all initial reports of ANC less than $1500/\mu\text{L}$ (ANC $< 1000/\mu\text{L}$ for BEN patients) with a repeat ANC measurement within 24 hours h

lini a ly a iat (b) (4)

Monitor ANC in any patient reporting a fever (temperature of 38.5°C or 101.3°F or greater) during the 2 weeks after discontinuation.

Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.

For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for General Population patients until their ANC is greater than or equal to $1500/\mu\text{L}$ and for Patients with BEN until their ANC is greater than or equal to $1000/\mu\text{L}$ or above h their baseline.

Refer to Section 2.4 of the clozapine Prescribing Information for further information.

Can a patient be rechallenged with clozapine?

Yes. For some patients who experience, or have experienced, moderate clozapine-related neutropenia (ANC less than $1000/\mu\text{L}$) or severe clozapine-related neutropenia (ANC less than $500/\mu\text{L}$), the risk of serious psychiatric illness from discontinuing clozapine may be greater than the risk of rechallenge. This may be relevant for patients with severe schizophrenic illness who have no treatment option other than clozapine.

In making the decision to rechallenge a patient, consider:

- a hematology consult

- the ANC ranges defined in the full Prescribing Information

- the patient's medical and psychiatric history

- a discussion with the patient and his or her caregiver about the benefits and risks h of clozapine rechallenge

- the severity and characteristics of the neutropenic episode

Re e o Secti n 2.5 R -initiation of Treatment in the e Prescribing Information for more information on how to restart Clozapien in patients who have discohtinued clozapine.

Website Screen Shots h

General me n

- Overall the website looked easy to navigate to find information. Below are some general and specific comments and recommendations for improvement.
- Revise the website is consistent with FDA's comments provided on May 22, 2015.
- In the next round of screen shots, provide screen shots that show the contents of the drop down menus. It is difficult to review and assess the website without being able to understand what choices/options a stakeholder has.

1.1 Home Page: pdf page 9

- There is a substantial amount of reverse text on the home page. This makes it difficult to read the screen. Reverse text is always more difficult to read and should be avoided outside of short headings. Revise the white text font size so that text is clearer.
- Revise the three steps for prescribers and for pharmacies to be consistent/identical to the steps on the corresponding stakeholder-specific landing pages (see pdf pages 15 and 17). Or, explain why the certification steps on the home page and stakeholder-specific landing pages should be different.
- Remove the Important Safety Information (ISI) tab from the home page and relocate the ISI to the "Resources" tab/page that contains all the prescribing information for the individual clozapine products.

The ISI is currently being reviewed and will be provided under a separate cover.

- Include a "Bookmark this page" icon in upper right-hand corner of the home page, as this website will be an important place for prescribers/other stakeholders to return.
- Underline the R-E-M-S when first referring to the REMS under the question, *What is the Clozapine REMS Program?* Revise the statement as follows under the "What is the Clozapine REMS Program?" - "A Risk Evaluation and Mitigation Strategy (REMS) is a strategy...."
- Will the "What's New?" tab be available after the transition period? If so, for how long?

1.2 - 1.6 Site Guide Page : pdf page 10-14

- We note that there are [Prescriber] Desi nee and Pharmacy Staff site guide tabs under the Support tab. Explain why these tabs are not included on the home page for these audiences as well. It may not be intuitive for the prescriber desi nee or authorized representative to click on the appropriate tab.
- Delete or revise the following statement "The links located at the top and bottom of every page offer information for prescribers, pharmacists, and patients. Additional information about the program is also available under Resources and through the FAWs, Site Map, and Contact Us links." The links for prescriber's pharmacists and patients do not appear on the bottom of the page.

1.4 Patient Education : pdf pag 12

- Explain where users will be directed once they click the **Learn More** button.

1.7 Prescriber Certification : pdf pag 15

- Insert text that explains to prescribers (and pharmacists) that they do not have to complete certification in one session.

1.8 Prescriber Designation Certification : pdf pag 16

- Update the text and materials according to recent alignment about Prescriber Designation training.

1.9 Pharmacy Certification : pdf pag 17

- Add "by the authorized representative" to the following sentence: "Certification in the Clozapine REMS Program includes completion of the following three steps by the authorized representative."
- It is not clear from the screenshots provided where (or how) within the website (more specifically within the pharmacy tab) the following pharmacy sub-stakeholders groups navigate the website to access and complete their respective training requirements: :
 - (1) pharmacists in non-switch pharmacy training (record of their training/completion of the KA is maintained), vs
 - (2) pharmacy staff enrollment (to gain access to the website but do not need to complete the education/KA), vs
 - (3) authorized representatives of pharmacists who are want to certify a pharmacy.

The website/pharmacy tab needs to allow these sub-groups to easily navigate to the information that is relevant to them.

1.11 Pharmacy Staff Enrollment: pdf pag 19

- Add text to clarify the difference between pharmacy staff enrollment, the authorized representative's enrollment, and pharmacists' education and knowledge assessment. Also refer to similar comment on pdf page 17 (above).

1.12 Patient Information : pdf pag 20

- Revise to more patient friendly/plain language text, as this tab is for patients. For example, use wording consistent with the Guide for Patients and Caregivers.
- Define neutropenia on this page using plain language terms from the Guide for Patients and Caregivers.

1.13 Program Materials: pdf pag 21

- Remove the Professional Societies tab with Letter to Professional Societies, as they are not needed by others outside of their original distribution.

1.16 FAQs: pdf pag 24

- When developing responses to the FAQs, we recommend the responses be consistent with content from the approved REMS materials

3.1 Create an Account: pdf page 33

- It is not clear from the screenshots how the "create an account" page relates to the user experience on the website. It is not clear how you navigated to the page or why it is necessary to use a create an account link. Is this specific to a particular group of anyone who visits the website expected to (allowed) create an account? If an account is created, what does it allow the user to do?
- Clearly who is allowed and who needs a create an account (list roles)

4.1 Prescriber Certification – Prescriber Intake: pdf page 36

- A screenshot of the certification process does not clearly suggest why the user is asked to view the "dshboard?" We note on these screenshots the "my dashboard" button is visible/available (as well as throughout the education program webpages) and appears unclear on many screenshots that the user is able to successfully click. Clearly the dashboard button is unclear, when the user becomes unclear, and what does the user expect to be able to do or what the user expects to be able to do.

We understand the user is with "create" process will have access to the dashboard to manage the user/create process to complete certification. This question is with regard to the user who is not part of the "guidance" process.

5.1 Prescriber Designee Certification: pdf page 40

- Explain where designees provide information about the prescriber/she is associated with. The screenshot does not include how this information is captured online or how the user is expected to be confirmed as having been properly notified of the online experience.

5.3 Prescriber Designee Attestation: pdf page 42

- Review the "responses" to be consistent with the May 22, 2015 comments
- Review the following statement, "By checking this box, I acknowledge that I will comply with the Clozapine REMS Program requirements. I hereby state that I have submitted sufficient information." This statement is consistent with the execution of the Designee Enrollment Form sent to CPMG on May 22, 2015
- Delete the following checkboxes from the box of responses: (b) (4)

(b) (4)

(b) (4) These statements are redundant with the responses noted above.

6.1 Pharmacy Certification – Role Selection: pdf page 44

- The descriptions of the Chain Pharmacy and the Outpatient Pharmacy are not clear.

For Chain Pharmacy Headquarters - explain "contracted" and consider including "Outpatient" to "Chain Pharmacy Headquarters".

For Outpatient Pharmacy - Based on our understanding that the authorized representative for an outpatient pharmacy for a "chain" could be directed to complete this enrollment form in the following instances: (1) if the chain is not contracted with the switch provider (and does not want to enter into a contract) and/or (2) if the chain does not plan to use switch technology for clozapine. Therefore, the definition should state that an authorized representative of an outpatient pharmacy is not affiliated with a "corporate pharmacy chain" contracted with the switch provider **OR** does the outpatient pharmacy(ies) does not have switch capability. In addition, the description implies that this option only applies to an "individual outpatient pharmacy" when this is not the case. Revise to explain that multiple locations can be enrolled through this mechanism.

Consider re-ordering the bullets so the outpatient bullets appear together then the inpatient.

Revise the webpage to address these issues.

- The webpage does not explain what an authorized representative must do if the authorized representative represents both inpatient and outpatient pharmacies. Does the authorized representative have to enroll twice - once for each pharmacy type or is there a mechanism to do both in single certification process? Add text to the page to address this issue.

6.2 Role Section Confirmation: pdf page 45

- Provide the pop-up boxes for chain headquarters and out-patient pharmacy. Those screenshots were not provided.

6.4 Authorized Representative Confirmation

- This statement, "... (b) (4) implies that the authorized representative (b) (4) when this is not the case (b) (4) (b) (4)

Revise this statement. For example: "Congratulations! You have successfully completed the required authorized representative training. You can now certify pharmacy locations."

6.5 Pharmacy Intake: pdf page 48

- What additional information, if any, appears based on the answer to this question "can your pharmacy management system adjudicate claims online? In other words, if the authorized representative selects "no" -- do the attestations for obtaining a PDA online appear?

In the screen shots provided, there are no attestations for the Item #12 on the Pharmacy Enrollment Form regarding the PDA.

Revise these screenshots to be consistent with the comments provided May 22, 2015 and include screens shots with an explanation with how the attestations related to the PDA are functionalized on the website.

6.6 Pharmacy Attestation: pdf page 49

- Does the authorized representative have to complete the attestation screen for every pharmacy location?

The attestations regarding PDA (electronic vs online) vs in-patient do not appear on the screenshot. What type of pharmacy attestation is this example for and where do those attestations reside? The do not appear on page 48 or 49 of the pdf.

- Delete the following text at the bottom of the box of attestations:

(b) (4)
(b) (4)
(b) (4) These statements are redundant with the attestations noted above them.

7.1 Pharmacy Search: pdf page 51

- This screen shot does not provide any direction to the "pharmacy staff" if they need to associate with more than one pharmacy location. Revise to ensure staff can associate with multiple pharmacy locations.

7.4 Pharmacy Staff Attestation: pdf page 54

- Revise this section to incorporate and be consistent with the "pharmacy staff" (b) (4) (b) (4) revisions sent to CPMG on May 22, 2015. We understand that associating with a certified pharmacy occurs before this screen. Incorporate and revise accordingly. We also note agreement to replace (b) (4) with "enrollment."

Pharmacy Staff can access the Clozapine REMS Program online to do the following:

- Enter an ANC for a patient,
- verify a prescriber is certified in the Clozapine REMS Program
- verify a patient is enrolled in the Clozapine REMS Program, (b) (4)
- obtain a pre-dispense authorization.

For online access to perform the above tasks, you must (b) (4)

By (b) (4) you agree not to share your credentials for the Clozapine REMS Program website or allow others to sign into the website using your credentials.

As part of your (b) (4) you must select the certified pharmacy location(s) where you fill and/or dispense clozapine. It is your responsibility to update this information as necessary.

8.1 Education Program: pdf page 56

- Revise the education program to be consistent with the revisions provided on May 22, 2015.

- We note the ongoing sections of the Guide for HCPs were omitted from the online versions on:
 - I am at least developed as a ever, or score can be managed?
 - How score appears discounted or neutropenia?
 - How score appears monitored or appears treatment side discounted?
 - Can a patient be recommended to appear?
 - What do I tell my patients about appearance?
 - How do I enroll a patient?
 - What my patients have been treated to appear before?
 - How do I find out my patient assisted in the NNRMF?
 - How do I report ANC results or my patients?
 - How do I authorize continuation of appearance in my patient's ANC session than 1000 or less than 500?
 - What my appearance patients under hospice care?
- What is a PDA?
- How do I verify that patients authorized to receive appearance?

For each section listed above, explain why the section is not important or the prescriber to review in the online education program. In addition, include the rationale for creating a standardized education experience or stakeholders cooperate to complete the training online vs on paper.

- We note that the sections of the Guide for HCPs on references "requirements or prescribers" not the overview bullets. Has the online education program been tailored to prescribers and the pharmacy education program side different? Please explain your intent and provide rationale your intent is to create the education programs specific to the stakeholder group.
- Explain the online "education program" be accessed without creating an account first.
- Are HCPs allowed to read the HCP Guide as part of their certification process - or must they view the web-based education program in order to access the online knowledge assessment? Both options should be clearly provided for stakeholders. Currently, the steps note that they must first read the HCP Guide before taking the knowledge assessment. It should also state they could complete the online education program as another option before taking the knowledge assessment.
- We recommend that the online education program be designed to require a certain amount of time spent on each page before clicking "next".
- Explain ongoing this process take to complete the "education program" and "knowledge assessment" and that has to be done in one sitting.

Reverse the webpage to include the estimated time it takes for a prescriber or pharmacist to complete the education program and knowledge assessment online. Please also include instructions on what happens if training is interrupted. Can the progress be saved?

z

9.1 Know Assessment: p f pa 73

- Clarify if there is a time limit in बनाम्पसो complete knowledge assessment.

10.1 Patient Enrollment: p f pa 88

- We note on this page that the “patient” tab is “highlighted” in purple. It appears a patient can begin to enroll themselves. Please explain why it appears this is part of the “patient” tab and clarify, as necessary, that they do not have the capability to enroll themselves in the REMS Program.

11.3 Dashboard Descriptors: p f pa 94

- NNRMF: This description of NNRMF is not adequate to convey to the reader what “NNRMF” is. Revise to provide more information to the user. For example, hyperlink the “NNRMF” so that a pop-up box will appear providing a short definition of NNRMF (as it appears in the HCP Guide) and include a graphic of the red flag in the example for visual association with what appears in the dashboard.
- “Interrupted”, “Pre-remission”, and “Incomplete” terms: explain how users find the definitions of these terms.
- With regard to “view laboratory,” explain the planned data retention of ANCs for patients. For example, how many years of data will be maintained?

97 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a r r s a i f a l c r i c r c r d h a w a s s i g d
l c r i c a l l y a d h i s a g i s h m a i f s a i f h l c r i c H
s i g a u r .

/s/ H

----- H

VASANT A S AYALASOMAYAJULA
06/16/2015

From: t [Kumme usan](#)
To: [Ayalasomayajula Vasantha](#)
Subject: t RE: REMS submission 3 - FDA Comments fo CPMG
Date: Friday May 22 2015 9:43:50 AM

Dear Vasantha,

Thank you. I have forwarded the information to [t](#) ^{(b) (4)} who will forward to the other companies.

Enjoy the sunshine and have a great weekend.

Susan [t](#)

Susan Kummerer
GPRD
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7781130
Fax +1 973 7813966
susan.kummerer@novartis.com
www.novartis.com

From: Ayalasomayajula Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Friday May 22 2015 7:34 AM
To: Kumme usan; Ka imattam, Albin; D Matino Jim
Cc: J nkins Da ll; Flow s Louis; Ha ison T y
Subject: REMS submission 3 - FDA Comments fo CPMG
Importance: High

Dear Susan,

Please see below for our comments to CPMG. Also provided these same comments as a pdf for CPMG.

Here is a list of the attached materials in Word/rtf. [t](#)

1. **REMS Document**
2. Prescriber Enrollment Form
3. Prescriber Designee Enrollment Form
4. Chain Headquarters Pharmacy Enrollment Form
5. [t](#) Pharmacy Enrollment Form
6. Pharmacy staff attestation language
7. Patient Enrollment Form
8. ANC Lab Reporting Form
9. Overview for HCPs
10. Guide for HCPs
11. Knowledge Assessment for HCPs
12. Guide for Patients and Caregivers
13. **REMS Supporting Document**
14. Dear Prescriber Letter
15. Dear Pharmacist Letter

- 16. What with Clozapin – An Overview
- 17. FDA comment on CP 5.22.15 (pdf)

We are providing comment on all the material submitted to FDA on April 17, 2015 with the exception of the MSRE Attachment Plan (which is part of the Supporting Document. We have provided it to the rest of the Supporting Document). Comment on MSRE Attachment Plan will be provided no later than Friday, May 29, 2015.

Please DARRT them mail as you have been doing.

I am off tomorrow. If you have any question, please call me at (b)(6) M

M
Thank you,
Suzann

+++++

1 COMMENTS FOR THE CPMG

1.1 PRESCRIBER DESIGNEE

M

With regard to the Prescriber Designation, we have the following comment:

- A. We align with the CPMP position to include a simplified training and assessment as part of the Prescriber Designation Enrollment process. The online training will consist of the responsibility and program requirement listed in the Prescriber Designation Enrollment Form (attached). Following this training, the assessment will consist of the following question: "I have reviewed the requirement of the Clozapine MSRE Program. Yes/No." If the designee clicks "No" they may be directed to the previous slide. A parallel paper process can be accomplished by the prescriber designee completing the enrollment form (attached). The inclusion of "By signing this form you will act on behalf of the certifying prescriber (identified below) to comply with the Clozapine MSRE Program requirement. I understand, M..." creates a parallel process to the online training and assessment format. If you believe additional training is necessary beyond that identified above, it can occur outside of and separate from the Clozapine MSRE and MSRE Prescriber Designation Enrollment process.
- B. Append the Prescriber Designation Enrollment Form to the MSRE Document and describe this component fully in the MSRE Supporting Document.

1.2 BEN DESIGNATION

M

We do not believe the program design aligns with labeling. The MSRE program design may result in unnecessary interruption for a patient with BE who has been diagnosed and confirmed by the prescriber at the time of enrollment. We agree with the approach described during the meeting on May 21, 2015 to implement an interim solution. This approach requires the prescriber (or designee) to change the treatment status for "interrupted" to "active" and auto-populate the "treatment rationale" drop-down box. This proposal allows the prescriber designee to continue treatment for a patient with BE who has an AC indicating moderate uterine prolapse. However, it still requires the prescriber or designee to perform an additional step that the labeling does not support.

M

We expect the program design will be corrected as soon as possible without impacting the target action date.

1.3 REMS DOCUMENT

- A. As the R [redacted] document is reviewed within the Agency, additional revisions have been made. We find the revisions to be clarifying and editorial in nature and not fundamentally changing any aspect of the program or R [redacted] document. The edits are in track changes along with comments.
 - B. Prescriber designee: Append the Prescriber designee enrollment Form to the R [redacted] document and T describe this component in the R [redacted] reporting document.
 - C. Implementation system: Provide your proposed percentage of pharmacies you plan to audit within one year and every two years thereafter. The R [redacted] document needs to reflect this agreed percentage.
- . See revised R [redacted] document.

1.4 REMS MATERIALS

The FDA review process included input from two health communications analysts and three pharmacists; this included a pharmacist and HCA who were not familiar with the clazapine R [redacted]. We attempted to revise the materials to illustrate formatting/spacing. However, tables, coloring, and formatting may have shifted in transition.

T
We find the revisions we provided to be clarifying and are not intended to fundamentally change aspects of the program. Rather, the materials were reviewed considering first the intended purpose of the piece and then revised to be as clear, constructive and as concise as possible while adequately explaining various requirements and functions. If you identify that revisions fundamentally change the program design, identify these revisions so we can further discuss.

1.4.1 Prescriber Enrollment Form

T
See revised Prescriber enrollment Form.

1.4.2 Prescriber Designee Enrollment Form

T
See revised Prescriber designee enrollment Form.

1.4.3 Pharmacy Enrollment Form

T
Revise the enrollment Form to delineate more clearly the out-patient and in-patient responsibilities.

Minor edits to the attestations with the exception of delineating the in-patient responsibilities. See revised Pharmacy enrollment Form.

1.4.4 Chain Headquarters Pharmacy Enrollment Form

T
Minor edits. See revised Pharmacy enrollment Form.

1.4.5 Patient Enrollment Form

Minor edits. See reviewed Form.

1.4.6 ANC Lab Reporting Form

T
The "Instructions for Prescribers" section did not reference the requirement to obtain a PAF for outpatient dispensing. See revised ANC Lab Reporting Form.

1.4.7 Guide for HCPs

- A. The FDA engaged in a message mapping process along with direct input from two health

communication and at least three pharmacists. Based on their expertise, we provide substantial quality content (plain language), formatting, and design review.

B. Delete reference to the Chain Headquarter Pharmacy Enrollment Form. Given the planned direct outreach to chain pharmacies that 1) have a contractual relationship directly with the provider, and 2) have enrolled in one or more of the regional registries, including information about the Chain Headquarter Pharmacy Enrollment Form and additional confusion without it.

C. See the review Guide for HCP.

1.4.8 Overview for HCPs

See review Overview.

1.4.9 Knowledge Assessment for HCPs

Minor edit. See review Knowledge Assessment.

1.4.10 Guide for Patients

Minor edit. See review Guide for Patient.

1.4.11 Pharmacy Staff Attestation Language

Given the limited nature of what the pharmacy staff can do in the system and the ultimate purpose of this aspect of the program, it is more accurate to describe this as an enrollment. Considering the enrollment of the pharmacy staff and agreement to implement staff training.

If you have concerns, request a teleconference for further discussion.

1.4.12 REMS Website

Append applicable comments provided in the other materials to the website. Comments on the screen shot submitted March 8, 2015 will be provided under separate cover.

1.4.13 Transition Plan Materials

For the materials, the FDA engaged in a message mapping process along with direct input from two health communication analysts (HCA) and three pharmacists. Based on their expertise, we provide substantial formatting and design review.

- A. Consistent with the Agency's Round 1 comment, separate the letter to be specific to takeholders (precriber separate from pharmacist). The purpose of the letter is to act as a "notice" providing high-quality information and introduce two key messages: 1) the new share program, 2) the new treatment/monitoring recommendation. The "goal" of this letter is fit the most critical information in a readable, user-friendly format on a single page.
- B. Apply the formatting and design comments from the Guide to HCP to the transition materials to 1) improve the readability and 2) provide a consistent experience for takeholders.
- C. Review the Dear Professional Society Letter to be identical in content appropriate to the takeholders group the society represents.
- D. See attached Letter for Pharmacist, Letter for Precriber, and "What's New with C Ozapine: An Overview"

1.4.14 REMS Supporting Documents

- A. Review the document thoroughly to provide definitions of terms.
- B. REMS Assessment Plan: The Assessment Plan is being actively discussed. Comments on the Assessment Plan will be provided under separate cover no later than May 29, 2015. If you have concerns, request a teleconference for further discussion.
- C. See revised Supporting Document.

1.4.15 Outstanding Items

- A. Prescriber Designee alignment
- B. BEN Designation – final solution
- C. Audit Plan: We understand you plan to submit the proposed Audit Plan 90 days after approval of the REMS. However, we must understand the percentage of pharmacies you propose to audit as detailed in the REMS Document.
- D. REMS Assessment – under review.
- E. Website screenshots – under review.

GENERAL COMMENTS

Resubmission Requirements and Instructions: Once you have received comments on the REMS document, submit the amended REMS (e.g., REMS document and all REMS materials) and the amended REMS Supporting Document. Provide a MS Word document with track changes and clean MS Word versions of all revised materials and documents.

Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format and PDF. It makes review of these materials more efficient.

C

Please let me know if you have any questions or comments.
Thanks and have a great day.

*****C*****

Sincerely,
Vasanth Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov C

This is a r r s a i f a l c r i c r c r d h a w a s s i g d
l c r i c a l l y a d h i s a g i s h m a i f s a i f h l c r i c H
s i g a u r .

/s/ H

----- H

VASANT A S AYALASOMAYAJULA
05/28/2015

From: c Aya a ya u a, Va antha
To: c [Kunere, Susan \(kunere@n.vard \)](mailto:kunere@n.vard)
Cc: [Jenkin, Darre](mailto:jenkin@n.vard); [DeMartin, Jifrida \(demartin@n.vard \)](mailto:demartin@n.vard); [Ferwer, Lui](mailto:ferwer@n.vard); [Harri, Terry](mailto:harri@n.vard)
Subject: Inf r t i raReque t a f w-up t CPMG ide pre entati n during the February 18, 2015 tee nferen e
Date: Wedne day, Mar h 04, 2015 12:21:00 PM

Dear Susan,

On February 18 and 26, 2015 FDA and CPMG held two teleconferences. The purpose of these meetings were for CPMG to present the items they have identified as having a “high impact” on the development and design of the single shared system REMS (SSSR) for clozapine based on the comments FDA provided on their December 23, 2014 proposed SSSR submission.

C

Information Request

C

The program areas listed below represent some of the areas of ongoing questions and discussion. We expect further discussion on these program areas during the March 11-12, 2015 face-to-face meeting.

1. Transition Plan

- a. The Agency will provide CPMG feedback on the transition plan proposal as soon as senior management has evaluated the plan.
- b. CPMG proposes utilizing the migrated pharmacy data to perform targeted outreach campaigns instructing pharmacies how to certify in the program and perform safe use functions before the PDA is implemented. There are no plans to complete analysis on the clozapine dispense data prior to REMS approval.

The Agency clarified that information on pharmacy type and identifying which pharmacies will be most impacted by the SSSR implementation is in line with the “dispense data” we are referring to. Updating the Agency on the outreach plans and the data used to inform the decision about how to target outreach is important to share. It improves confidence we have that the transition will be successful and minimize disruption.

(b) (4) will discuss with CPMG what (and when) data can be provided to the C Agency.

c. Product Return/Pullback

We agree that how product is returned to individual sponsors can vary based on individual manufacturer’s product return policies. However, when product must be returned must be consistent across all sponsors.

Product return is an important aspect of the transition plan. Existing product on pharmacy shelves in non-certified pharmacies needs to be addressed to ensure the safe use of clozapine.

2. Treatment Rationale

a. Patients with BEN

Prescribers should not be required to provide a reason to continue treatment if the patient has BEN and has an ANC between 500-1000. The labeling states that treatment

does not need to be notified. Thus, a prescriber does not need to enter a treatment quantity at the node to continue treatment in that ANC range. Please confirm the REMS system reflects labeling and does not require completion of a treatment quantity for patients with BEN who have an ANC between 500-1000 to avoid unnecessary treatment notification.

b. Duration of treatment

During the February 18, 2015 teleconference you explained that the prescriber determines the duration of the treatment quantity. In the present design, the prescriber has 3 options to choose from: 1) indefinite, 2) embedded consistent with the monitoring frequency, 3) set a time frame/date



Explain if a prescriber must re-assess a continuous treatment in the following scenario: Patient on chemotherapy, with each chemotherapy cycle the patient's ANC drops < 1000 and rebounds into the normal range. Does the prescriber have to re-assess (provide the treatment quantity) each time the ANC drops after it has recovered? In other words, does the treatment quantity stay in place regardless of the ANC or if the ANC recovers then drops below 1000, does that trigger the need for the prescriber to reassess a continuous treatment?

3 ANC Reporting

As a follow-up item, explain the process you plan for a hospital patient with moderate/severe neutropenia. Would the prescriber need to continue ANC reporting to the SSSR node for the patient to continue on clozapine?

4 Prescriber Designee

The prescriber designee should not Provide an update on the timeline impact with re-designing the system

5 Inpatient REMS process

The Agency explained a lack of understanding of how information would be exchanged between inpatient and outpatient settings to avoid continuity of care issues for patients when they are transitioning between settings. CPMG explained when a patient transitions to an inpatient setting and back to an outpatient setting, the change in prescriber would require the patient to be re-enrolled (even if back to the previous outpatient prescriber). This re-enrollment alerts the system with regard to who to re-estimate information from (e.g., ANC). The Agency expressed concern regarding the re-enrollment burden placed on prescribers and the likelihood that alerts would be sent to the wrong prescriber enrollment under a new prescriber does not occur, patients taking home medications, etc. Moreover, the Agency stated that the essential component of inpatient hospitalists that directs them NOT to discontinue clozapine if the prescriber is not associated with the patient in the system and

we do not believe it necessary from a feasibility perspective.

As you discussed in the proposed, consider requiring the npatent pharmacist to report the npatent tatur and npatent pharmacist at the same time the npatent pharmacist refer to at the patent and pharmacist are enrolled in the Cozapine REM program would part of the address some of the transition challenges.

Expand the response to the proposed npatent process including the alert, role and response of each take order – inpatient, outpatient pharmacist, npatent pharmacist, outpatient pharmacist, npatent pharmacist, and patient. Include a scenario in your expansion similar to the education during the teleconference on February 26, 2015. A part of the scenario, expand the impact on the take order (and follow-up process) for a patient with an ANC < 500 who is hospitalized and remains hospitalized and finally rebounded.

6. Website demonstration

During the March 11-12, 2015 face-to-face meeting, provide a demonstration of the website based on the functionality developed to date.

We note the following are additional outstanding items that we have no further comment at this time but will be addressed in the future:

- AE Reporting
- REM Assessment Plan

Thank You.

S

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov S

This is a r r s a i f a l c r i c r c r d h a w a s s i g d
l c r i c a l l y a d h i s a g i s h m a i f s a i f h l c r i c H
s i g a u r .

/s/ H

----- H

VASANT A S AYALASOMAYAJULA
03/06/2015

From: c [Ayaaya, Vaantha](#)
To: c [Kunere, Susan \(kunere@nva.gov \)](#)
Cc: c [Jenkins, Darre](#); [Fisher, L ui](#); [Harri n, Terry](#); [DeMartin, rji \(rjademartin@nva.gov \)](#)
Subject: c FW: C zapine SSSR - Content and Material TO GO TO CPMG
Date: c Friday, February 06, 2015 4:37:00 PM
Attachments: [C zapine Prepared REMS document draft 2.5.15 to CPMG.docx](#)
[C zapine REMS ANC Reporting Form Fina 2014 12 23 \(2\).docx](#)
[C zapine REMS HCP Guide Fina 2014 12 23.docx](#)

Susan,

The following comments (pasted below) are from DRISK.

In addition, please provide them the following 3 pieces

- REMS Document
- ANC Reporting Form
- Guide for HCPs

+++++

1 COMMENTS FOR THE CPMG c

1.1 REMS DOCUMENT

As the REMS Document is reviewed within the Agency, additional revisions have been made. We find the revisions to be clarifying and editorial in nature and not fundamentally changing any aspect of the program or REMS Document.

During the review process, changes were accepted to the REMS Document. Unfortunately, a track change document cannot be provided at this time. However, we have noted/highlighted sections where the text has changed. After you have the opportunity to review the REMS Document, please let us know what, if anything, is concerning so we can discuss.

See revised REMS Document.

1.2 REMS MATERIALS c



(b) (4)



Apply applicable comments provided in the other materials to the website.

1.2.4 Outstanding Issues

The following issues are outstanding and pending agreement between the Agency and CPMG (

- Transition Plan
 - Overall proposal is under review with senior management in the Agency.
 - A proposed plan for cooperative product return/push back as part of the Transition Plan has not been presented to the Agency
 - Analysis of cooperative registration by pharmacy type is ongoing with CPMG (plan will be presented to the Agency once complete).

- REMS Processes and Requirements

- on the h

(b) (4)

- 'Dosing information' from Pharmacies

In the outpatient setting, it is often unclear that the following dosing information will be required and obtained either electronically through the 'switch' or manually via the website or verbally to the call center; 'non-switch): (

- Dispense date
- NDC
- Days' supply (

- Quantit
- c ib id ntifi

In th pati nt tting, what info mation will b obtain d i not cl a . Weag obtaining a p -di p n autho ization i not n c a in th inpati nt tting. We do not full und tand ou p opo al fo inpati nt u and po ting qui mnt and how it will n u th EMS i abl to t ack who i an inpati nt. We und tand th conc n ou ai d with ho pital having to app ov multipl fo ms

Ba d on ou und tanding of th EMS and inpati nt p opo al, w b li v it i n c a fo af u fo th p og am to c iv th following fom th pha mac : a li t of inpati nt who a c iving clozapin and th i admit dat , di cha g dat and acknowl dg mnt that ach pati nt continu to c iv clozapin . We continu to b li v that po ting ANC hould b th p ima pon ibilit of th p c ib .

o T atment ational /autho ization to continu clozapin t atment.

- Web it d mon t ation
- Di t ibuto En ollm nt

Weag that a Di t ibuto En ollm nt Fo m i acc ptabl . We do plan to p ovid comment on Di t ibuto En ollm nt und pa at cov .

- Audit lan
- EMS A ment lan

o Wehav not ta t d di cu ion ga ding th cont nt of th A ment lan

GENERAL COMMENTS

ubmi ion qui ment and In t uction : Onc ou hav c iv d comment on th EMS docum nt, ubmit th am end d EMS (.g., EMS docum nt and all EMS mat ial) and th am end d EMS Suppo ting Docum nt. ovid a MS Wo d docum nt with t ack chang and a cl an MS Wo d v ion of all vi d mat ial and docum nt .

Submit th EMS and th EMS Suppo ting Docum nt a two pa at MS Wo d Fo mat qu t: Submit ou p opo d EMS and oth mat ial in MS Wo d fo mat and DF. It mak vi w of th mat ial mo ffi nt.

Sincerely,
Vasantha Ayala
 Senior Regulatory Project Manager
 Office of Surveillance and Epidemiology | Project Management Staff
 Ph: 240-402-5035 (O)
 Email: Vasantha.ayalasomayajula@fda.hhs.gov

APPEARS THIS WAY ON
ORIGINAL

This is a r r s a i f a l c r i c r c r d h a w a s s i g d
l c r i c a l l y a d h i s a g i s h m a i f s a i f h l c r i c H
s i g a u r .

/s/ H

----- H

VASANT A S AYALASOMAYAJULA
02/17/2015

From: c Aya a ya u a, Va antha
To: c [Kunere, Susan \(Susan.kunere@va.gov\)](mailto:kunere@va.gov)
Cc: c [Jenkins, Darre](#); [Fisher, L ui](#); [Harri n, Terry](#)
Subject: c C zapine_REMS_Pre ribemnt_F r Fina_2014_12_23.d x, C zapine_REMS_Guide f r Patient and Caregiver_Fina_2014_12_23.d x, C zapine_REMS_Patientmnt_F r Fina_2014_12_23.d x, C zapine_REMS_Pre riber_De ignee_Enr
Date: c Thursday, January 22, 2015 12:05:00 PM
Attachments: [C zapine_REMS_Pre ribemnt_F r Fina_2014_12_23.d_x](#)
[C zapine_REMS_Guide f r Patient and Caregiver_Fina_2014_12_23.d_x](#)
[C zapine_REMS_Patientmnt_F r Fina_2014_12_23.d_x](#)
[C zapine_REMS_Pre riber_De ignee_Enr nt_F r Fina_2014_12_23_br.d](#)

Dear Susan,
Please see the REMS documents that are attached which have been reviewed by FDA. c

1. C zapine_REMS_Pre ribemnt_F r Fina_2014_12_23.d_x
2. C zapine_REMS_Guide f r Patient and Caregiver_Fina_2014_12_23.d_x
3. C zapine_REMS_Patientmnt_F r Fina_2014_12_23.d_x
4. C zapine_REMS_Pre riber_De ignee_Enr nt_F r Fina_2014_12_23_br.d

Thank you,

Sincerely,
Va antha Aya a
Senior Regulatory Product Manager
Office of Surveillance and Epidemiology | Product Management Staff
Ph: 240-402-5035 (O)

mailto:Va antha.aya a ya u a@fda.hhs.gov c

This is a r r s a i f a l c r i c r c r d h a w a s s i g d
l c r i c a l l y a d h i s a g i s h m a i f s a i f h l c r i c H
s i g a u r .

/s/ H

VASANT A S AYALASOMAYAJULAH
02/05/2015

From: c Aya a ya u a, Va antha
To: c [Kunere, Susan \(Susan.kunere@va.gov\)](mailto:kunere_susan@va.gov)
Cc: c [Jenkins, Darre](#); [Fisher, L. J.](#); [Mackay, Cristina](#); [Harri n, Terry](#)
Subject: c C zapi ne - Materia review ed fr DRISK t CPMG
Date: c M nday, February 02, 2015 9:09:00 AM
Attachments: [C zapi ne RE MS Chain Phar m y m r nt F r Fina 2014 12 23 \(1\).d](#)
[C zapi ne RE MS HCP Overview Guide Fina 2014 12 23 \(1\).d_x](#)
[C zapi ne RE MS HCP Kn wedge n Ae e nt Fina 2014 12 23 \(1\).d_x](#)
[C zapi ne RE MS Phar m y m r nt F r Fina 2014 12 23.d_x](#)

Susan,
C

Please see the following (attached) materials from DRISK.

1. Chain Pharmacy Enrollment Form
2. Pharmacy Enrollment Form
3. Overview of HCPs
4. Knowledge Assessment for HCPs

Additional materials will be sent to you this week.

Thanks,
Vasantha C

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

C

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/s/ H

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VASANT H A S AYALASOMAYAJULA H
02/05/2015 H

From: Ayalasomayajula, Vasantha
To: sherice.mills@jazzpharma.com; jennifer.ekelund@jazzpharma.com
Cc: [Jenkins, Darrell](#); [Flowers, Louis](#); [Harrison, Terry](#)
Subject: Clozapine REMS IR - Monitoring Frequencies
Date: Wednesday, December 02, 2015 2:31:00 PM
Attachments: [rev Ltr to Comm Ostroff from Pharmacist re Clozapine REMS Redacted.pdf](#)
[LATH 120115 165718.pdf](#)
[CPMG IR 12.2.15 monitoring frequency.doc](#)
Importance: High

Dear CPMG,

Please see the attached Information Request and two letters (one to the commissioner and the other from a prescriber). Please note that we plan to discuss this at tomorrow's tcon in addition to the IR that was sent yesterday. We have not received anything with regard to CPMG's plan to communicate that the pharmacy certification deadline (12/14/15) has been extended. We did not receive any communication to the Agency for review (if you planned to seek our input as you did with the prescriber certification extension).

Thank you.
Vasantha

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

To: CPMG

IR: Override for clozapine monitoring frequency

Within the last day, FDA received two formal letters regarding inaccurate monitoring frequencies for purportedly stabilized, long-term clozapine patients in the Clozapine REMS Program. Please review the attached letters.

While this issue is known, we are receiving an increasing number of complaints regarding this issue. As we are all aware, there have been several data migration failures during the operationalization of the Clozapine REMS Program. One of these data migration failures is migration of lab data; specifically if a patient is missing one lab draw result then they are automatically converted to a weekly monitoring schedule despite the patient being on a monthly monitoring schedule prior to being migrated into the system. Currently, it is our understanding that a prescriber must complete extensive manual data recording to correct a patient's monitoring frequency and there is no override capabilities to revert the patient back to their previously acceptable monitoring frequency. This is not only a burden on the healthcare delivery system but puts an already at-risk patient population at risk for access issues and gaps in therapy.

In light of the fact you determined the migrated data is unreliable, the REMS Program needs a process in place that accepts the prescriber's assertion with regard to the patient's monitoring frequency and consider what, if any information, the prescriber needs to provide (e.g., signed affirmation regarding the patient's clozapine treatment duration, stable ANC during the treatment duration, and/or most recent ANC result, etc). At the same time we believe it is important to educate prescribers that moving forward an ANC commensurate with the patient's monitoring frequency needs to be provided to the Clozapine REMS Program to avoid future problems.

The Agency considers this a high priority safety concern.

By December 9, 2015 propose a plan for how to address this issue including a timeline to resolution. Include the following in your plan:

- Address the problem as an "important update" on the Clozapine REMS Program website by close of business Friday, December 4, 2015. This communication should explain the problem and state you are working on a new solution. Submit the proposed language for review.
- Once agreed upon, update to the "important update" on the Clozapine REMS Program website outlining the steps a prescriber must take if the prescriber asserts the patient's monitoring frequency is incorrect.

(b) (6)

Psychiatry

November 5, 2015

Telephone (b) (6)

Clozapine REMS Program
P. O. Box 29058
Phoenix, AZ 89038-9058

RE: (b) (6)
Enrollment ID (b) (6)

Dear Sir or Madam:

This patient has chronic psychosis with Parkinson's disease and that is the reason she has been on Clozaril 50 mg. daily since the 1990's.

I have been informed by her pharmacy that your program is requiring the ANC to be done weekly in her case. I do not have any idea why she should have weekly ANC's since she has been stable for a number of years and she has never had a problem before with the blood count.

This requirement causes unnecessary time and paperwork, not to mention the distress to the patient and the possible disruption of medication therapy and the potential for relapse if it becomes necessary to switch medications due to the above requirements.

As I have been unable to reach a representative on your phone line despite numerous attempts, waiting for hours and not getting through, I am sending this letter to express my deep concerns over this issue. Please investigate this and respond promptly to me. I am forwarding a copy of this letter to the FDA as well.

Yours sincerely,

(b) (6)

(b) (6)

Copy to:
FDA
MedWatch
5600 Fishers Lane
Rockville, MD 20857
Copy to Modern Pharmacy

November 20, 2015

Stephen Ostroff, M.D., Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

15-7452

Re: Clozapine REMS Program

Dear Commissioner Ostroff :

We have been working with Clozapine and the special mental health population that uses it since it came to market over 20 years ago. As you know, patients who require Clozapine are a special subset of the mental health community who either did not tolerate or did not respond to more traditional therapy. These patients can be high risk in terms of their stability in the community without Clozapine.

The original monitoring program was put in place to protect patients from leukopenia, a rare but serious side-effect. Over our 20 plus years and hundreds of Clozapine patients, I have only seen a few cases of this and the program picked them up.

The new national Clozapine REMS program is currently being implemented. It puts into place some fairly rigid rules for lab work and dispensing of Clozapine. All of us involved in dealing with this population certainly do not want to compromise patient safety in any way and welcome change that improves patient care. However, some of the rules seem to be arbitrary and actually do impede patient care. For example, the new REMS program requires a patient to drop back to weekly lab draws if they miss a lab for any reason. In fact, they actually require retrospectively that if a patient missed a lab in the last 12 months, they have to drop back to weekly labs. As you can imagine, getting this population to a lab for blood work is very challenging even for every 28 day draws much less weekly labs. To penalize a patient for a missed lab seems to be arbitrary and counter to good patient care.

There are other valid reasons why patients may miss a lab including lab requests that expire without the patient knowing it, lab samples that clot, patients who are on vacation, patients who miss lab visits because they are sick or due weather and transportation issues. If the patient has had stable labs, it does not make therapeutic sense to penalize the patient and insist on weekly labs. We do not want the new REMS program to create barriers that impede patients from receiving this critical therapy.

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I do not recall their being a period of public comment on the new REMS rules so I am requesting now that you allow clinical judgment to be used by those of us who have years of experience with this drug and this population. Again, patient safety is and always has been the paramount concern for this population.

Thank you for your time and assistance.

Sincerely,

(b) (6)

Pharmacist

(b) (6)

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/s/

VASANTHA S AYALASOMAYAJULA
12/03/2015

From: Ayalasomayajula, Vasantha
To: sherice.mills@jazzpharma.com; jennifer.ekelund@jazzpharma.com
Cc: [Jenkins, Darrell](#); [Flowers, Louis](#); [Harrison, Terry](#)
Subject: Clozapine: Response to Implementation Timeline Extension
Date: Tuesday, December 01, 2015 4:21:00 PM

Dear Sherice,

FDA acknowledges the CPMG's determination that the migrated registry data is not representative of the current universe and disposition of prescribers, pharmacies, and patients. FDA further recognizes the importance of establishing this denominator and the disposition of stakeholder relationships to minimize patient access issues.

In response to your proposed timeline sent via email on Tuesday, November 24, 2015 and presented during the teleconference on Wednesday, November 25, 2015, we cannot agree with the proposed milestones because 1) your timeline does not take into account certain important issues that need to be addressed and 2) it is not acceptable to wait until March to start collecting data to establish the current universe and disposition of stakeholders. With these concerns in mind, we have the following comments/questions. Provide a response in writing by **December 8, 2015**.

1. Revise the timeline to accommodate the following high priority issues to improve the usability and accessibility of the registry and to reduce burden to the healthcare system:
 - a. Less restrictive patient search capabilities (i.e. zipcode)
 - b. Develop a single account login for users who assume multiple roles within the Clozapine REMS Program that does not require a stakeholder to have different email addresses
 - c. Incorrect monitoring frequency designation for patients transitioned from previous registries to the new database
 - d. Modifications to the REMS regarding inpatient prescriber certification requirements
 - e. Incorporating the VA into the Clozapine REMS Program
 - f. Improved tracking of unresolved or "open" customer tickets within the Contact Center
 - g. Need for NCPDP number to certify as a pharmacy
 - h. Protected Health Information (PHI) privacy concerns
2. In the timeline provided, the CPMG will approve modified business requirements by February 4, 2016, a full two months after the Agency is asked to provide feedback to the CPMG. Explain what activities are occurring in these two months and include any barriers to the Sponsors approving the modified business rules sooner than the currently proposed date.
3. The soft-launch of the PDA needs to occur as early as possible to begin data collection to better inform the metrics needed to assess the denominator of stakeholders leading up to a new deadline for certification into the REMS Program.
 - a. It is not clear why pharmacy and prescriber data cannot be collected now through the eligibility check process currently in place (online or through the call center). If this cannot be accommodated now, explain why.
 - b. Can the PDA can be implemented (e.g., "turned on") through the switch in a passive manner for data collection that would not provide feedback to the pharmacy sooner than mid-March? If this is not possible, explain why. Implementing passive data collection now while developing the new business rules that can be implemented in the future seems to be a better use of time than delaying any data collection until March after all business rules have been developed.
4. Leveraging the PDA to obtain pharmacy specific information should be augmented with

distribution data obtained individually from all clozapine Sponsors. As discussed in the 11/23 t-con, information requests will be sent to each individual Sponsor to gather and provide the Agency with data generated by distributors detailing the distribution of clozapine in the year prior to the SSS approval.

5. Consider and propose how you intend to augment the prescriber and patient data obtained thru the PDA (online, call center or switch PDA). Distributor data can be utilized to augment pharmacy data but you have not proposed any alternative ways to augment patient and prescriber data.
6. Propose a deadline for prescriber and pharmacy certification. We understand the need to use metrics not yet available to be able to ensure that the date chosen will be as accurate as possible; however, not having a date by which stakeholders must be registered is a substantial disincentive to interact with the system.

Thank you,
Vasantha

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VASANTHA S AYALASOMAYAJULA
12/02/2015