

Initial Shared System Approval: 09/2015
Most Recent Modification: 02/2021

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

1. Certain Healthcare Providers who prescribe clozapine are certified

- a. All Healthcare Providers who prescribe clozapine for outpatient use must be certified.
- b. All Healthcare Providers who prescribe clozapine to a patient who is not yet enrolled must be certified.
- c. To become certified to prescribe clozapine, 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 *Clozapine REMS Knowledge Assessment for Healthcare Providers*; and,

- iii. Enroll in the Clozapine REMS Program by completing the *Clozapine REMS Prescriber Enrollment Form*.
- d. 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 *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia* 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 *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia*
 - 2.) Completing the *Clozapine REMS Patient Enrollment Form* for each patient. Submit the completed form to the Clozapine REMS Program
 - ii. Perform the following requirements on an ongoing basis for each patient and submit to the Clozapine REMS Program via the online system, by fax, or by calling the Clozapine REMS Program Contact Center:
 - 1.) Order ANC according to the monitoring schedule described in the Prescribing Information
 - 2.) Submit ANC according to the patient's monitoring frequency on file with the Clozapine REMS Program as described in the Monitoring Schedule of the Prescribing Information:
 - a) For weekly monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 7 days of the lab draw date
 - b) For every two weeks monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 15 days of the lab draw date
 - c) For monthly monitoring frequency, ANC must be submitted to the Clozapine REMS Program within 31 days of the lab draw date
 - 3.) Provide authorization of treatment for patients (i.e., Treatment Rationale) with an ANC that falls below the acceptable range described in the Prescribing Information, when the prescriber determines the benefits outweigh the risks of developing severe neutropenia
 - 4.) Verify the patient monitoring frequency on file with the Clozapine REMS Program is aligned with the patient's monitoring frequency as described in the Prescribing Information

e. Clozapine Sponsors must:

- i. Ensure that Healthcare Providers who prescribe clozapine as described in II.A.1.a-b are 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 as described in II.A.1.a-b 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 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 as described in II.A.1.a-b 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, and 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*
- *Clozapine REMS Knowledge Assessment for Healthcare Providers*
- *Clozapine REMS Prescriber Enrollment Form*
- *Clozapine REMS Prescriber Designee Enrollment Form*
- *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia*
- *Clozapine REMS Patient Enrollment Form*
- Clozapine REMS Program Website

2. Pharmacies that dispense clozapine are certified

Outpatient Pharmacies

- a. To become certified to dispense clozapine, outpatient pharmacies must:
 - i. Designate an authorized representative to complete certification on behalf of the pharmacy using the appropriate form:
 - 1.) *Clozapine REMS Outpatient 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 *Clozapine REMS 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 *Clozapine REMS Knowledge Assessment for Healthcare Providers*
 - iii. Put processes and procedures in place to ensure the following requirements are completed:
 - 1.) Obtain a Predispense Authorization each time from the Clozapine REMS Program by accessing the Clozapine REMS Program Website, Clozapine REMS Program Contact Center, or enabling the pharmacy management system to support communication with the Clozapine REMS Program system
 - 2.) 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 or a third party acting on behalf of the Clozapine Sponsors

- 3.) Recertify in the Clozapine REMS Program every two years
- 4.) Comply with audits by the Clozapine Sponsors or a third party acting on behalf of the Clozapine Sponsors 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. Pharmacies that support electronic communication verification with the Clozapine REMS Program system must:

- 1.) Ensure the pharmacy enables its pharmacy management system to support communication with the Clozapine REMS Program system using established telecommunication standards and runs validation test transaction(s) to validate the system enhancements
- 2.) Dispense clozapine to patients only after obtaining a Predispense Authorization each time by processing all clozapine prescriptions, including cash claims, through their pharmacy management system to electronically:
 - a.) Verify the prescriber is certified in the Clozapine REMS Program
 - b.) Verify the patient is enrolled in the Clozapine REMS Program
 - c.) Verify the ANC is current (within 7 days of the Predispense Authorization transaction date for weekly monitoring, 15 days for every two weeks monitoring and 31 days for monthly monitoring)
 - d.) Verify the ANC is within the acceptable range described in the Prescribing Information, or that a certified prescriber has authorized clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits outweigh the risks of developing severe neutropenia
 - e.) Report dosing information for each clozapine prescription/fill to the Clozapine REMS Program

ii. Pharmacies that do not support electronic telecommunication verification with the Clozapine REMS Program system must dispense clozapine to patients only after obtaining a Predispense Authorization each time by accessing the Clozapine REMS Program Website or calling the Clozapine REMS Program Contact Center to:

- 1.) Verify the prescriber is certified in the Clozapine REMS Program
- 2.) Verify the patient is enrolled in the Clozapine REMS Program

- 3.) Verify the ANC is current (within 7 days of the Predispose Authorization transaction date for weekly monitoring, 15 days for every two weeks monitoring, and 31 days for monthly monitoring)
- 4.) Verify the ANC is within the acceptable range described in the Prescribing Information, or that the certified prescriber has authorized clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits outweigh the risks of developing severe neutropenia
- 5.) Report dosing information for each clozapine prescription/fill to the Clozapine REMS Program

Inpatient Pharmacies

- c. To become certified to dispense clozapine, inpatient pharmacies must:
 - i. Designate an authorized representative to complete the certification process on behalf of the pharmacy using the *Clozapine REMS Inpatient 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 *Clozapine REMS 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. Each pharmacist must be trained by reviewing *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers* and successfully completing the *Clozapine REMS Knowledge Assessment for Healthcare Providers*
 - iii. Put processes and procedures in place to ensure the following requirements are completed prior to the initial inpatient dispensing of clozapine:
 - 1.) Perform an Eligibility Check from the Clozapine REMS Program by accessing the Clozapine REMS Program Website or contacting the Clozapine REMS Program Contact Center to verify the patient is enrolled in the Clozapine REMS Program
 - 2.) Obtain a current ANC by accessing the Clozapine REMS Program Website, contacting the Clozapine REMS Program Contact Center, or by accessing the inpatient medical record
 - 3.) Verify that the ANC is within the acceptable range described in the Prescribing Information or that the prescriber has authorized clozapine treatment for patients

with an ANC that falls below the acceptable range when the prescriber determines the benefits outweigh the risks of developing severe neutropenia

- 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 or a third party acting on behalf of the Clozapine Sponsors
- v. Comply with audits by the Clozapine Sponsors or a third party acting on behalf of the Clozapine Sponsors to ensure that all processes and procedures are in place and are being followed for the Clozapine REMS Program

d. As a condition of certification, inpatient pharmacies must:

- i. Dispense clozapine only after:
 - 1.) Performing an Eligibility Check by accessing the Clozapine REMS Program Website or calling the Clozapine REMS Program Contact Center to verify the patient is enrolled in the Clozapine REMS Program;
 - 2.) Verifying that the patient's ANC obtained from the Clozapine REMS Program Website, the Clozapine REMS Program Contact Center, or the patient's inpatient medical record is current; and,
 - 3.) Verifying that the ANC is within the acceptable range described in the Prescribing Information or that the prescriber has authorized clozapine treatment for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits outweigh the risks of developing severe neutropenia
- ii. Dispense no more than a 7-day temporary supply of clozapine to an enrolled patient upon discharge from the healthcare facility

e. Clozapine Sponsors must:

- i. Ensure that pharmacies that dispense clozapine are certified, in accordance with the requirements described above
- ii. Ensure that authorized representatives can complete the pharmacy certification process and 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. Ensure that pharmacies renew certification in the Clozapine REMS Program every two years
- v. Verify every two years that the authorized representative's name and contact information corresponds to that of the current designated authorized representative for

the certified pharmacy; and if different, require the pharmacy to recertify 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*
- *Clozapine REMS Knowledge Assessment for Healthcare Providers*
- *Clozapine REMS Inpatient Pharmacy Enrollment Form*
- *Clozapine REMS Outpatient 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 *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia* unless clinical judgment indicates that the patient's adherence to the treatment regimen will be negatively impacted by providing *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia*
 - ii. Been informed by the prescriber of the risks of clozapine and the Clozapine REMS Program requirements, using *A Guide for Patients and Caregivers: What You Need to Know About Clozapine and Neutropenia*
- b. Clozapine Sponsors must:
 - i. Ensure that the certified prescriber can 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 Pharmacies that dispense clozapine are certified')

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

- a. Clozapine Sponsors must ensure that before dispensing clozapine the certified pharmacy can verify the ANC is current and,
 - i. Within the acceptable range described in the Prescribing Information; or,

- ii. The prescriber has authorized clozapine treatment (Treatment Rationale) for patients with an ANC that falls below the acceptable range when the prescriber determines the benefits outweigh the risks of developing severe neutropenia

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 the 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 severe neutropenia
- c. Clozapine Sponsors must ensure that patient enrollment can be completed via the 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. 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 or a third party acting on behalf of the Clozapine Sponsors 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. Monitoring distribution data and auditing 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
- 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 Clozapine REMS Program requirements
4. Clozapine Sponsors must ensure that pharmacies' REMS requirements are met and may decertify noncompliant pharmacies 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 pharmacies interfacing with the Clozapine REMS Program
7. Clozapine Sponsors must ensure that within 70 calendar days of approval of the <MMDDYYYY> REMS modification, the Clozapine REMS Program Website is fully operational and all materials listed in or appended to the Clozapine REMS Program document are available through the Clozapine REMS Program Website (www.clozapinerems.com) or by calling the Clozapine REMS Program Contact Center at 844-267-8678
8. The Clozapine REMS Program Website (www.clozapinerems.com) must continue for the duration of the REMS. Additionally,
 - a. The Clozapine REMS Program Website must include the following online capabilities for certified Healthcare Providers, their designees, or pharmacy staff, as applicable:
 - i. completion of prescriber and pharmacy certification,
 - ii. enrollment and management of patients,
 - iii. provision of Predispense Authorizations; and,
 - iv. provision of Eligibility Check results
 - b. The Clozapine REMS Program Website must include the option to print versions of the Clozapine REMS Program materials
 - c. The individual, product-specific clozapine websites for Healthcare Providers must include a prominent REMS-specific link to the Clozapine REMS Program Website
9. Clozapine Sponsors must continuously monitor the certified pharmacies to ensure the 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 pharmacies 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. Initial pharmacy audit must be implemented within 180 days following approval of the current Clozapine REMS modification;
 - b. Subsequent audits will be administered every two years thereafter; and,
 - c. 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

III. Timetable for Submission of Assessments

Clozapine NDA Sponsors must submit REMS Assessments annually beginning February 28, 2020. 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 conclude 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.