

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. 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*
- 2.) 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.
- 2.) 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 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
 - 4.) 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 all clozapine prescriptions, 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/fill 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 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 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 REMS requirements.

4. Clozapine Sponsors must ensure that pharmacies' REMS requirements are met and may de-certify 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 all materials listed in or appended to the Clozapine REMS document are available through the Clozapine REMS Program website www.clozapinerems.com or by calling the Clozapine REMS Program contact center.
8. The Clozapine REMS Program website (www.clozapinerems.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 healthcare professionals 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. 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.

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 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.