



FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines

Safety Announcement

[09-15-2015] The U.S. Food and Drug Administration (FDA) is making changes to the requirements for monitoring, prescribing, dispensing, and receiving the schizophrenia medicine clozapine, to address continuing safety concerns and current knowledge about a serious blood condition called severe neutropenia. Severe neutropenia is a dangerously low number of neutrophils, white blood cells that help fight infections. Severe neutropenia can be life-threatening.

Treatment with clozapine may improve the symptoms of schizophrenia in patients who do not respond adequately to standard antipsychotic treatments. Symptoms of schizophrenia include hearing voices, seeing things that are not there, and being suspicious or withdrawn. Clozapine is also effective in reducing the risk of repeated suicidal behavior in patients with schizophrenia or schizoaffective disorder. We previously communicated safety information associated with clozapine in [February 2011](#).

There are two parts to the changes in the requirements for treating patients with clozapine. First, we have clarified and enhanced the prescribing information for clozapine that explains how to monitor patients for neutropenia and manage clozapine treatment. Second, we approved a new, shared risk evaluation and mitigation strategy (REMS) called the Clozapine REMS Program. The revised prescribing information and the Clozapine REMS Program will improve monitoring and management of patients with severe neutropenia. The shared REMS is also expected to reduce the burden and possible confusion related to having separate registries for individual clozapine medicines. The requirements to monitor, prescribe, dispense, and receive all clozapine medicines are now incorporated into the Clozapine REMS Program.

The Clozapine REMS Program replaces the six existing clozapine registries maintained by individual clozapine manufacturers. The shared REMS requires prescribers, pharmacies, and patients to enroll in a single centralized program. Patients who are currently treated with clozapine will be automatically transferred to the Clozapine REMS Program. In order to prescribe and dispense clozapine, prescribers and pharmacies will be required to be certified in the Clozapine REMS Program according to a specific transition schedule starting *October 12, 2015* (see Additional Information for Prescribers section and Additional Information for Pharmacies section for more details).

The monitoring recommendations for neutropenia caused by clozapine treatment have changed. Clozapine can decrease the number of neutrophils in the blood, in some cases causing severe

neutropenia. As described in the revised clozapine prescribing information, and in the Clozapine REMS Program, neutropenia will be monitored by the absolute neutrophil count (ANC) only, rather than in conjunction with the white blood cell count. Moreover, in the Clozapine REMS Program, the requirements for ANC are being modified so that patients will be able to continue on clozapine treatment with a lower ANC, a change that will allow continued treatment for a greater number of patients. In addition, patients with benign ethnic neutropenia (BEN), who previously were not eligible for clozapine treatment, will now be able to receive the medicine. The revised prescribing information facilitates prescribers' ability to make individualized treatment decisions if they determine that the risk of psychiatric illness is greater than the risk of recurrent severe neutropenia, especially in patients for whom clozapine may be the antipsychotic of last resort.

We urge health care professionals, patients, and caregivers to report side effects involving clozapine medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Facts about Clozapine

- Manufacturers of approved clozapine medicines include HLS Therapeutics USA, Jazz Pharmaceuticals Inc, Sun Pharmaceutical Industries Inc, Teva Pharmaceuticals USA, and Mylan Pharmaceuticals Inc. Clozapine is also sold under the brand names Clozaril, FazaClo, and Versacloz.
- Starting October 12, 2015, clozapine will only be available through the Clozapine REMS Program. Clozapine is an antipsychotic medicine used to treat schizophrenia in patients whose symptoms are not controlled with standard antipsychotic treatment. It is also used to treat recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.
- Treatment with clozapine may help improve the symptoms of schizophrenia in patients, such as hearing voices, seeing things that are not there, and being suspicious or withdrawn. Clozapine is also effective in reducing the risk of repeated suicidal behavior.
- During 2014, a nationally estimated number of approximately 90,000 patients received dispensed prescriptions for clozapine from outpatient retail pharmacies in the U.S.¹

Additional Information for Patients and Caregivers

- FDA is making changes to the way patients treated with the schizophrenia medicine clozapine are monitored. These changes are being made to address continuing concerns and current knowledge about severe neutropenia, a serious blood condition associated with clozapine.
- Starting October 12, 2015, clozapine will be available only through the Clozapine REMS Program. Your prescriber and pharmacy must be certified to prescribe and dispense clozapine.
- Patients currently being treated with clozapine will be automatically transferred to the new Clozapine REMS Program. Your doctor is responsible for making sure you are enrolled in the Clozapine REMS Program.

- Visit the Clozapine REMS Program website (www.clozapinerems.com) for more information described in *What You Need to Know about Clozapine and Neutropenia: A Guide for Patients and Caregivers*.
- Report any side effects from using clozapine to the FDA MedWatch program, using the information at the bottom of the page in the “Contact Us” box.

Additional Information for Prescribers

- The prescribing information for clozapine has been revised to incorporate new requirements for prescribing clozapine and monitoring patients for neutropenia.
- The requirements to monitor, prescribe, dispense, and receive clozapine are now incorporated into the new, shared Clozapine REMS Program, which replaces the six individual clozapine registries. The REMS program includes all clozapine medicines in order to provide a centralized point of access for prescribers and pharmacists in managing the risk of neutropenia. Starting October 12, 2015, clozapine will be available only through the Clozapine REMS Program.
- Important changes to the neutropenia monitoring recommendations and treatment algorithm for clozapine include:
 - Absolute neutrophil count (ANC) is the only test result accepted in the Clozapine REMS Program to monitor for neutropenia:
 - If the patient is an outpatient, the ANC must be reported to the Clozapine REMS Program before clozapine is dispensed.
 - If the patient is an inpatient, the ANC must be reported within 7 days of the most recent blood sample.
 - Patients with benign ethnic neutropenia (BEN) can now be treated with clozapine.
 - There are two ANC monitoring algorithms:
 - **For general population patients**, i.e., those without benign ethnic neutropenia (BEN), interrupt treatment if neutropenia is suspected to be clozapine-induced for ANC less than 1,000 cells per microliter.
 - **For patients with BEN**, interrupt treatment if neutropenia is suspected to be clozapine-induced for ANC less than 500 cells per microliter.
 - Although re-challenging patients who develop severe neutropenia during treatment with clozapine is not recommended, under the revised prescribing information prescribers will have more flexibility to make individualized treatment decisions for their patients if they determine that the risk of psychiatric illness is greater than the risk of recurrent severe neutropenia.
 - The National Non-Rechallenge Master File (NNRMF) will be discontinued on October 12, 2015. Patients were listed in the NNRMF if they had a WBC less than 2,000 cells per microliter or an ANC less than 1,000 cells per microliter.
 - All patients listed in the NNRMF will be automatically transferred to the Clozapine REMS Program and clearly identified.
- Prescriber Certification in the Clozapine REMS Program

- Starting *October 12, 2015*, health care professionals who wish to prescribe clozapine to outpatients or inpatients must be certified in the Clozapine REMS Program. To become certified in the Clozapine REMS Program, prescribers must:
 - Review the prescribing information for clozapine,
 - Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*,
 - Successfully pass the *Knowledge Assessment for Healthcare Providers*, and
 - Complete and submit the one-time *Clozapine REMS Prescriber Enrollment Form*.
- Prescribers can be certified through the Clozapine REMS Program website at www.clozapinerems.com, or by faxing completed forms to 844-404-8876. For more information or to request materials, call the Clozapine REMS Program at 844-267-8678.
- Prescribers who currently treat patients with clozapine will have additional time to complete their certification and will have access to the Clozapine REMS Program to manage current patients. The Clozapine REMS Program will contact current prescribers to provide instructions on how to access the Clozapine REMS Program website.
- Prescribing Clozapine
 - Managing existing patients:
 - All patients registered in any of the existing clozapine registries within the last three years and all patients listed in the NNRMF will be automatically transferred into the Clozapine REMS Program.
 - Starting *October 12, 2015*, prescribers will no longer be able to enroll or manage patients through the other clozapine patient registries. All patient management activities will be handled through the Clozapine REMS Program.
 - Managing new patients:
 - Prescribers must be certified in the Clozapine REMS Program in order to enroll new patients.
 - Generally, to enroll a new patient prescribers must:
 - Provide the patient or caregiver with *What you Need to Know about Clozapine: A Guide for Patients and Caregivers*,
 - Inform the patient or caregiver about the risk of severe neutropenia associated with clozapine and about the Clozapine REMS Program requirements, and
 - Complete and submit *Patient Enrollment Form*.
 - Prescribers can enroll patients through the Clozapine REMS Program website at www.clozapinerems.com, or by faxing the completed *Patient Enrollment Form* to 844-404-8876.
 - Prescribers may designate other health care professionals or office staff to enroll patients and enter ANC results on their behalf.

Report any adverse events involving the use of clozapine to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Additional Information for Pharmacies

- The prescribing information for clozapine has been revised to incorporate new requirements for prescribing clozapine and monitoring patients for neutropenia.
- The requirements to monitor, prescribe, dispense, and receive clozapine are now incorporated into the new, shared Clozapine REMS Program, which replaces the six individual clozapine registries. The REMS program includes all clozapine medicines in order to provide a centralized point of access for prescribers and pharmacists in managing the risk of neutropenia. Starting October 12, 2015, clozapine will be available only through the Clozapine REMS Program.
- Pharmacy Certification in the Clozapine REMS Program
 - Starting *October 12, 2015*, pharmacies must be certified in the Clozapine REMS Program to dispense clozapine to outpatients or inpatients. Pharmacies can no longer enroll or manage patients through the other clozapine patient registries.
 - To become certified, a pharmacy must designate an authorized representative to:
 - Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*,
 - Successfully pass the *Knowledge Assessment for Healthcare Providers*,
 - Complete and submit the appropriate *Clozapine REMS Pharmacy Enrollment Form*, and
 - Implement the necessary staff training and processes to comply with the Clozapine REMS Program requirements.
 - Pharmacies with multiple locations must certify on behalf of each pharmacy location, and add each pharmacy location as that pharmacy completes the necessary training. Pharmacies certify through the Clozapine REMS Program website (www.clozapinerems.com), or call the Clozapine REMS Program at 844-267-8678 for more information or to request materials.
- Except for prescriber designees, a pharmacist will no longer be able to enroll patients in the Clozapine REMS Program or view a list of patients on clozapine.
- Dispensing Clozapine
 - Starting *October 12, 2015*, pharmacies must be certified in the Clozapine REMS Program to dispense clozapine to outpatients or inpatients.
 - Starting *December 14, 2015*, in order to dispense clozapine, outpatient pharmacies are required to obtain a pre-dispense authorization (PDA) from the Clozapine REMS Program before clozapine can be dispensed. A PDA is an electronic code that indicates the Clozapine REMS Program has verified that the prescriber and pharmacy are certified and the patient is enrolled, and the patient’s ANC is acceptable or that the certified prescriber authorized the patient to continue clozapine treatment:
 - A PDA can be obtained one of three ways: 1) by enabling the pharmacy management system to support electronic communication with the Clozapine REMS Program, 2) by signing into the Clozapine REMS

Program website, or 3) by calling the Clozapine REMS Program at 844-267-8678.

- Inpatient pharmacies do not need to obtain a PDA.

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Reference

1. Source: IMS Health, Total Patient Tracker (TPT), Y2014, Extracted AUG2015.
2. Dunk LR, Annan LJ, and Andrews DC. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. *British Journal of Psychiatry* 2006;188:255-263.