FDA Removes Risk Evaluation and Mitigation Strategies (REMS) Program for the Antipsychotic Drug Clozapine

Neutropenia Risk Remains, but REMS No Longer Necessary and REMS May Prevent Treatment Access

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What Is FDA Announcing?
The U.S. Food and Drug Administration (FDA) removed the risk evaluation and mitigation strategy (REMS) for clozapine (currently marketed as Clozaril, Versacloz, and generics), effective June 13, 2025. Clozapine, an antipsychotic medicine, can cause severe neutropenia (a low level of certain white blood cells), which can lead to serious and fatal infections. The removed REMS required enrollment of prescribers, pharmacies, and patients in a restricted distribution program and reporting of the level of certain white blood cells (i.e., the absolute neutrophil count (ANC)) to mitigate the risk of severe neutropenia.

Based on FDA's re-evaluation of the Clozapine REMS and on the November 19, 2024 Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee, the Agency determined that the REMS was no longer necessary to ensure the benefits of clozapine outweigh the risk of severe neutropenia. Although there remains a risk of severe neutropenia with clozapine use, clozapine labeling (including a new Medication Guide) is sufficient to mitigate this risk and maintain a positive benefit/risk profile. ANC monitoring can help identify neutropenia early to allow for timely intervention. Therefore, prescribers should continue to monitor patients' ANC according to the monitoring frequencies described in the prescribing information. Eliminating the REMS is expected to improve access to clozapine and decrease the burden on the health care delivery system.

What Is FDA Doing?
FDA has removed the REMS for clozapine. As a result, prescribers, pharmacies, and patients are no longer required to participate in the REMS program and report patients' ANC results to the REMS in order for clozapine to be dispensed to the patient.

Information about severe neutropenia is in the prescribing information for all clozapine medicines, including in a Boxed Warning and a new Medication Guide.

Severe neutropenia remains a serious, potentially fatal risk that is greatest in the first several months of clozapine treatment. ANC monitoring can help identify neutropenia early to allow for timely intervention. Therefore, FDA recommends that prescribers monitor patients' ANC according to the monitoring frequencies described in the prescribing information.

What Is Clozapine, and How Can It Help Me?
Clozapine is an atypical antipsychotic medicine used to treat people who are severely ill with schizophrenia who remain symptomatic on other schizophrenia medicines. Clozapine is thought to work by balancing the brain's levels of dopamine and serotonin, two neurotransmitters involved in brain

function. Clozapine is also approved to treat people with schizophrenia or schizoaffective disorder who have been suicidal and may be at risk for recurrent suicidal behavior.

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Clozapine is an oral tablet that patients take either once or twice a day. Its most common side effects are sleepiness or drowsiness, headache, dizziness, shaking movements (tremors), heart and blood vessel problems, low blood pressure, fast heartbeat, a lot of saliva in your mouth, passing out (syncope), dry mouth, increased sweating, constipation and nausea, vision problems, and fever.

The most serious side effects are severe neutropenia (very low white blood cell counts) that can lead to serious infection and death; decreased blood pressure, slow heart rate, or syncope that can lead to death; seizures; serious heart problems; and increased risk of death in people with dementia. Regarding severe neutropenia, the risk appears to be greatest in the first several months of clozapine treatment, but the risk never goes away. Frequent absolute neutrophil count (ANC) monitoring is necessary to identify neutropenia early so that health care professionals can intervene.

What Should Patients and Caregivers Do?

Patients should be aware that they no longer need to be enrolled in the REMS to receive clozapine. That means that pharmacies no longer need to verify patients' enrollment in the REMS and patients' absolute neutrophil count (ANC) before dispensing clozapine.

However, patients should talk with their health care professional about the need for monitoring ANC before starting clozapine and during treatment, including the frequency of lab testing. Patients should be aware that they may need to modify, pause, or stop clozapine treatment based on results of ANC monitoring. Patients should contact their health care professional if they notice symptoms of neutropenia such as:

- Flu-like symptoms
- Wounds that take a long time to heal
- Fever or chills
- Skin, throat, vaginal, urinary tract, or lung infection
- Extreme fatigue or weakness
- Pain or burning while urinating
- Sores or ulcers inside the mouth or gums
- Unusual vaginal discharge or itching skin
- Sores or pain in the rectal area

- Abdominal pain or bloating

What Should Health Care Professionals Do?
Prescribers of clozapine no longer have to be enrolled in the REMS or to enroll their patients in it. They also do not have to submit absolute neutrophil count (ANC) results to the REMS program. Prescribers should continue to monitor their patients' ANC before starting clozapine and during treatment according to the prescribing information and to counsel patients about the risk of severe neutropenia. Pharmacies do not need to be enrolled in the REMS to order clozapine from wholesaler distributors. Pharmacists do not need to verify patient eligibility, including ANC monitoring, before dispensing clozapine to patients.
Health care professionals should be advised that the risk of neutropenia is generally greatest in the first several months of clozapine treatment and persists at a lower level thereafter. In addition, they should tell their patients to seek medical care if they experience symptoms that may indicate neutropenia.

What Did FDA Find?
FDA used a systematic, structured approach to re-evaluate the Clozapine REMS, which included collaborating on several studies to assess clozapine use and participants' adherence to monitoring, as well as neutropenia outcomes. This evaluation included a literature review, a review of the FDA Adverse Event Reporting System, and additional studies designed and analyzed in collaboration with Brigham and Women's Hospital, the U.S. Department of Veterans Affairs, and through the FDA Sentinel System.

This re-evaluation aimed to determine:

1. If the risk of severe neutropenia has changed since the initial approval of clozapine in 1989;
2. If health care professionals' knowledge of the risk of and need for monitoring has changed since 1989; and
3. The extent that health care professionals monitor patients' absolute neutrophil count (ANC) results.

Regarding the risk of severe neutropenia with clozapine use, FDA concluded that the risk appears to be greatest in the first several months of clozapine treatment but never reaches zero. This is consistent with the currently approved clozapine prescribing information, which states that the risk is greatest in the first 18 weeks of clozapine initiation. FDA's assessment confirmed that frequent ANC monitoring is necessary to identify neutropenia early so that health care professionals can intervene.

The re-evaluation found that prescribers appear to more broadly understand the risk of severe neutropenia and the need for ANC monitoring, and that medical training and health care systems have more widely incorporated information and training on clozapine and its safe use today compared to 1989. In addition, guidelines and resources available to prescribers about clozapine have greatly expanded since 1989.

In addition to FDA's evaluation, the Agency considered the advice of the November 19, 2024, Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee. In general, the committee members agreed with the continued need to monitor ANCs; however, they concluded that ANC documentation and training for health care

professionals through the REMS are no longer necessary to ensure safe use of clozapine. During the Advisory Committee's open public hearing, the Agency also heard from patients and caregivers that the REMS can sometimes impede access to clozapine.

Data Summary
Data to support the removal of the Clozapine REMS included a literature review, a review of the FDA Adverse Event Reporting System, and additional studies designed and analyzed in collaboration with Brigham and Women's Hospital, the U.S. Department of Veterans Affairs, and through the FDA Sentinel System. Together these studies capture 20 years of data from different types of health care delivery systems and insurance coverage. These data were presented and discussed during the November 19, 2024 Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee.

What Is My Risk?
All medicines may have side effects—even when used correctly as prescribed. People respond differently to medicines depending on their health, genetic factors, other medicines they are taking, and many other factors. As a result, it is difficult to determine how likely it is that someone will develop neutropenia after taking clozapine. Talk to your health care professional(s) if you have questions or concerns about the risks of taking clozapine.

How Do I Report Side Effects of Clozapine?
To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving clozapine or other medicines to the FDA MedWatch program using the information in the "Contact FDA" box at the bottom of this page.

How Can I Get New safety Information on Medicines I'm Prescribing or Taking?
You can sign up for email alerts about Drug Safety Communications on medicines or medical specialties of interest to you.