**US FDA Never Fully Enforced The Clozapine REMS. Now’s It’s Not Needed**

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The Risk Evaluation and Mitigation Strategy hindered access and burdened the health care system even though it was never fully implemented or enforced. The FDA still recommends prescribers monitor patients’ absolute neutrophil count to prevent severe neutropenia.



A patient advocacy group said the elimination of the REMS is the first domino to fall in improving clozapine access. (Shutterstock)

**Key Takeaways**

* The clozapine REMS program is no longer necessary to ensure the drug’s benefits outweigh the risk of severe neutropenia, the FDA said.
* The agency expects that eliminating the REMS will decrease the burden on the health care delivery system and improve access to the antipsychotic.
* The Angry Moms, a patient advocacy group, said the end of the REMS program is the “first domino to fall,” but an overhaul of clozapine’s labeling and other work still are needed.

The US Food and Drug Administration eliminated the Risk Evaluation and Mitigation Strategy for the antipsychotic clozapine, closing the book on a program that was never fully implemented or enforced, but still blamed for hindering access for thousands of schizophrenia patients.

“Beginning today, FDA does not expect prescribers, pharmacies, and patients to participate in the Risk Evaluation and Mitigation Strategies (REMS) program for clozapine or to report results of absolute neutrophil count (ANC) blood tests before pharmacies dispense clozapine,” the agency [announced](https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/frequently-asked-questions-clozapine-rems-modification) 24 February on its website.

“FDA still recommends that prescribers monitor patients’ ANC according to the monitoring frequencies described in the prescribing information,” the agency said. “Information about severe neutropenia will remain in the prescribing information for all clozapine medicines, including in the existing boxed warnings.”

The agency’s action aligns with the recommendation of two advisory committees that overwhelmingly concluded the REMS requirements for physician education and ANC results documentation were not necessary to ensure safe use.

**Adcomm Favored Elimination**

Clozapine is the only treatment approved for treatment-resistant schizophrenia and is also effective in reducing suicidality. However, the drug can cause severe neutropenia, potentially resulting in serious and fatal infections.

Since its initial approval, clozapine prescribing and distribution was restricted to mitigate neutropenia risk.

The REMS required prescriber education and certification, pharmacy certification and patient enrollment. Prescribers obtained baseline ANC results for a patient and monitored ANC levels at regular intervals during treatment. Documentation of blood test results through the REMS allowed the patient to receive clozapine.

However, the REMS was never fully implemented or enforced due to technical and operational challenges, as well as concerns about interrupting patient access to the drug. The FDA exercised its enforcement discretion, which allowed patients, prescribers and pharmacies to access clozapine outside of the REMS.

In briefing documents for a November 2024 advisory committee meeting, the Clozapine Product Manufacturers Group, which runs the shared REMS, [estimated that more than 64,000 patients](https://insights.citeline.com/pink-sheet/product-reviews/us-advisory-committees/is-a-clozapine-rems-still-needed-two-us-fda-adcomms-will-weigh-neutropenia-risk-mitigation-H3P6WKKSIBAERAQIY4BDAKJD3U/) have accessed clozapine even though not all of the REMS safe use conditions had been met. The FDA estimated that about 65% of outpatients treated with clozapine were participating in the REMS.

The REMS appeared headed for elimination after the drug safety/risk management and psychopharmacologic drugs [advisory committees voted 14-1](https://insights.citeline.com/pink-sheet/product-reviews/us-advisory-committees/clozapine-rems-a-barrier-to-treatment-and-unnecessary-for-safe-use-us-fda-adcomms-say-KDK6ICJKNBHPTBGVFFL3C6ME7U/) that the REMS requirements for prescribers to document ANC results and for the pharmacy to verify those results were unnecessary. The panels similarly voted that the requirement for health care providers to learn about the risk of severe neutropenia and the need for ANC monitoring was not necessary.

Advisory committee members said that although the REMS was well intentioned, it presented numerous obstacles to prescribing and access. The FDA’s enforcement discretion policy for the clozapine REMS also was not well understood.

Dozens of patient advocates testified about challenges accessing the drug, including physicians unwilling to prescribe clozapine because the requirements were too burdensome and pharmacies unwilling to dispense the drug absent ANC documentation.

Some advisory committee members said they were not familiar with the enforcement discretion policy and that health care practitioners and pharmacists were hesitant to prescribe or dispense the drug outside the REMS for fear of losing their license or being sued.

Panelists said prescribers should be trusted to read the drug’s label and follow the recommendations for regular ANC monitoring. They also said sufficient information about the risk of severe neutropenia and the need to conduct blood testing is available outside the REMS and that the prescriber education requirement was no longer necessary.

**Decrease Burden, Improve Access**

The FDA said that although the risk of severe neutropenia still exists, the REMS program is no longer necessary to ensure the drug’s benefits outweigh its risks.

“Eliminating the REMS is expected to decrease the burden on the health care delivery system and improve access to clozapine,” the agency said. “FDA has instructed the clozapine manufacturers to formally submit a modification to eliminate the clozapine REMS and to update the prescribing information, including removing mandatory reporting of ANC blood tests to the REMS program.”

The FDA said it will work with the clozapine manufacturers in the coming months to update the prescribing information and eliminate the REMS.

**‘More Work To Do’**

The Angry Moms, a group that has advocated for eliminating the REMS, said it was grateful that the FDA “finally heard us.”

“The end of the US clozapine REMS is the first domino to fall, but we have a lot more work to do,” the group told the Pink Sheet. Clozapine labeling needs an overhaul because the ANC monitoring requirements are outdated, and the fast titration schedule is “outright dangerous,” The Angry Moms said.

In addition, there is no clarifying guidance about the amount of ANC testing needed and when it is truly important.

“Physicians need permission to handle cases when the testing itself is a barrier, but clozapine is needed to save a life or to achieve meaningful recovery,” the group said. “Providers need significant training on current best practices. Psychiatrists are still tragically utilizing clozapine [as] a ‘last-line’ treatment, with the misperception that safer, more ‘modern’ alternatives exist.”

**Other REMS Programs Eliminated, Changed**

The clozapine advisory committee meeting raised questions about how the effectiveness of REMS programs are measured. Some suggested assessments also should look at the experience of individuals [who are not part of the REMS](https://insights.citeline.com/pink-sheet/product-reviews/us-advisory-committees/beyond-the-rems-clozapine-adcomm-shows-why-in-program-assessments-are-not-always-enough-LTRD6IJS5JFNPLQDVEQJAZLJZM/) to determine whether distribution restrictions hinder drug prescribing or use.

Clozapine joins several other REMS programs with distribution restrictions, also known as elements to assure safe use, that have been eliminated or significantly modified in recent years.

In September 2023, the FDA eliminated the REMS program for [Sebela Pharmaceuticals](https://insights.citeline.com/companies/sebela-pharmaceuticals-inc/%22%20%5Ct%20%22_blank)’ irritable bowel syndrome drug Lotronex (alosetron) and generics, which has been associated with serious gastrointestinal events, including ischemic colitis.

REMS assessment reports indicated acceptable knowledge and understanding among prescribers and patients related to the goal and objectives of the REMS. Adverse event reporting of ischemic colitis and serious complications of constipation has been stable, and an increase in severe outcomes has not been observed since the REMS was modified in 2016, the agency said.

An analysis of new female users of alosetron in the Sentinel Distributed Database from 2016 to 2020 also found the rate of ischemic colitis for alosetron consistent with that listed in the labeling, as well as an ongoing downward trend in the use of all alosetron products.

In November 2023, the agency directed isotretinoin manufacturers to [modify the iPLEDGE REMS](https://insights.citeline.com/PS149498/Isotretinoin-REMS-Modifications-Show-How-Advisory-Panel-Can-Push-FDA-To-Change-Its-Mind/) to minimize its burden on patients, pharmacies, and prescribers while maintaining the safe use of the acne drug, a teratogen.

Among the changes, the FDA eliminated the REMS requirement that pregnancy tests must be performed in a specially certified laboratory, allowing prescribers to use home pregnancy tests for their patients during and after isotretinoin treatment. The agency also removed a waiting period requirement for patients if they do not obtain isotretinoin within the first seven-day prescription window.

In January 2023, the FDA modified the REMS for the abortifacient mifepristone, removing the requirement for in-person dispensing and adding a certification requirement for pharmacies that dispense the drug.

The FDA’s relaxation of some mifepristone restrictions in 2016 and 2021 prompted a legal challenge that [went to the US Supreme Court](https://insights.citeline.com/PS154844/SCOTUS-Mifepristone-Decision-Sets-High-Bar-For-US-FDA-Suits-But-Risks-To-Agency-Authority-Linger/). In June, the high court ruled the plaintiffs lacked standing to bring the case.