Clozapine Monitoring
National Protocol Guidance
March 2025

VA Pharmacy Benefits Management Services, VA National Formulary Committee, and the National Clozapine Coordinating Center

Purpose: To provide general guidance on absolute neutrophil count (ANC) monitoring during clozapine initiation and maintenance treatment.

Disclaimer: To be consistent with the purpose of this general guidance and not to be overly proscriptive, this guidance allows facilities the flexibility to exercise modifications to the protocol as necessary to operationalize the use of clozapine and its monitoring.

Background

Clozapine is an atypical antipsychotic indicated for treatment-resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder.

On February 24, 2025, the FDA removed the REMS requirement for clozapine stating: "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. FDA still recommends that prescribers monitor patients' ANC according to the monitoring frequencies described in the prescribing information. Information about severe neutropenia will remain in the prescribing information for all clozapine medicines, including in the existing Boxed Warnings.
Although the risk of severe neutropenia with clozapine still exists, FDA has determined that the REMS program for clozapine is no longer necessary to ensure the benefits of the medicine outweigh that risk. Eliminating the REMS is expected to decrease the burden on the health care delivery system and improve access to clozapine. FDA has notified the manufacturers that the clozapine REMS must be eliminated. 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.
In the coming months, FDA will work with the clozapine manufacturers to update the prescribing information and eliminate the Clozapine REMS."

While the elimination of the Clozapine REMS no longer requires the reporting of ANCs, appropriate monitoring is still recommended. This protocol outlines the suggested ANC monitoring for the initiation and maintenance of clozapine treatment.

Departments Affected: Pharmacy, Psychiatry, Laboratory

Indications

- Treatment-resistant schizophrenia
- Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder

Contraindications

a. Hypersensitivity to clozapine or any other component of clozapine

Boxed warnings

a. Severe neutropenia
b. Orthostatic hypotension, bradycardia, syncope
c. Seizures
d. Myocarditis, pericarditis, cardiomyopathy, and mitral valve incompetence
e. Increased mortality in elderly patients with dementia-related psychosis

Precautions

a. Eosinophilia
b. QT interval prolongation
c. Metabolic Changes
d. Neuroleptic malignant syndrome
e. Hepatotoxicity
f. Fever
g. Pulmonary embolism
h. Anticholinergic toxicity
i. Interference with cognitive and motor performance
j. Use with caution in patients with decreased GI motility
k. Special populations
    a. Poor metabolizers of CYP2D6
        i. Smokers via CYP1A2 induction – with respect to forced absence during hospitalization

Dosing

a. Starting Dose: 12.5 mg once daily or twice daily
b. Use cautious titration and divided dosage schedule
c. Titration: increase the total daily dosage in increments of 25 mg to 50 mg per day, if well-tolerated
d. Target dose: 300 mg to 450 mg per day, in divided doses, by the end of 2 weeks
e. Subsequent increases: increase in increments of 100 mg or less, once, or twice weekly
f. Maximum daily dose: 900 mg

ANC Monitoring Recommendations

1. Obtain baseline ANC before treatment initiation
2. Treatment Recommendations for maintenance treatment
    a. Weekly from initiation to 6 months
    b. Every 2 weeks from 6 to 12 months (if the ANC remains in the normal range; ANC greater than or equal to 1500/μL for the general population, ANC greater than or equal to 1000/μL for patients with Benign Ethnic Neutropenia)
    c. Monthly after 12 months, using shared decision making (if ANC continues to remain in the normal range)

References

1. CLOZARIL (clozapine) [prescribing information]. Novartis Pharmaceuticals Corporation. Washington, DC 2017.
2. FDA Briefing Document. Risk Evaluation and Mitigation Strategy (REMS) for Clozapine Products Clozapine REMS. Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee. November 19, 2024.
3. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/frequently-asked-questions-clozapine-rems-modification. Accessed 3/21/2025.