

Indications and Important Selected Safety Information About Clozapine-Containing Products

INDICATIONS:

Clozapine is an atypical antipsychotic indicated for:

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

CONTRAINDICATIONS:

- Known serious hypersensitivity to clozapine or any other component of clozapine.

WARNING: SEVERE NEUTROPENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

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- Severe Neutropenia: Clozapine can cause severe neutropenia, which can lead to serious and fatal infections. Patients initiating and continuing treatment with clozapine must have a baseline blood absolute neutrophil count (ANC) measured before treatment initiation and regular ANC monitoring during treatment.
- Clozapine is available only through a restricted program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS) program.
- Orthostatic Hypotension, Bradycardia, and Syncope: Risk is dose-related. Starting dose is 12.5 mg. Titrate gradually and use divided dosages.
- Seizure: Risk is dose-related. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors for seizure.
- Myocarditis and Cardiomyopathy: Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions.
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis: clozapine is not approved for this condition.

WARNINGS AND PRECAUTIONS:

Eosinophilia

- Assess for organ involvement (e.g., myocarditis, pancreatitis, hepatitis, colitis, nephritis). Discontinue if these occur.

QT Interval Prolongation

- Can be fatal. Consider additional risk factors for prolonged QT interval (disorders and drugs).

Metabolic Changes

- Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
 - Hyperglycemia and Diabetes Mellitus: Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
 - Dyslipidemia: Undesirable alterations in lipids have occurred in patients treated with atypical antipsychotics.
 - Weight Gain: Significant weight gain has occurred. Monitor weight gain.

Neuroleptic Malignant Syndrome (NMS)

- Immediately discontinue and monitor closely. Assess for co-morbid conditions.

Fever

- Evaluate for infection and for neutropenia, NMS.

Pulmonary Embolism (PE)

- Consider PE if respiratory distress, chest pain, or deep vein thrombosis occur.

Anticholinergic Toxicity

- Use cautiously in presence of specific conditions (e.g., narrow angle glaucoma, use of anticholinergic drugs).

Interference with Cognitive and Motor Performance

- Advise caution when operating machinery, including automobiles.

USE IN SPECIFIC POPULATIONS:

- Discontinue drug or discontinue nursing, taking into consideration importance of drug to mother.

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DRUG INTERACTIONS:

- Concomitant use of Strong CYP1A2 Inhibitors: Reduce clozapine dose to one third when coadministered with strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, enoxacin).
- Concomitant use of Strong CYP3A4 Inducers is not recommended.
- Discontinuation of CYP1A2 or CYP3A4 Inducers: Consider reducing clozapine dose when CYP1A2 (e.g., tobacco smoke) or CYP3A4 inducers (e.g., carbamazepine) are discontinued.

ADVERSE REACTIONS

Most common adverse reactions (≥5%) were: CNS reactions (sedation, dizziness/vertigo, headache, and tremor); cardiovascular reactions (tachycardia, hypotension, and syncope); autonomic nervous system reactions (hypersalivation, sweating, dry mouth, and visual disturbances); gastrointestinal reactions (constipation and nausea); and fever.

To report SUSPECTED ADVERSE REACTIONS, contact the Clozapine REMS program at 844-267-8678 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DOSING AND ADMINISTRATION:

Required Laboratory Testing Prior to Initiation and During Therapy

- Prior to initiating treatment with clozapine, a baseline ANC must be obtained. The baseline ANC must be at least 1500/μL for the general population, and at least 1000/μL for patients with documented Benign Ethnic Neutropenia (BEN).
- To continue treatment, the ANC must be monitored regularly.

Initiating Treatment

- Starting Dose: 12.5 mg once daily or twice daily.
- Use cautious titration and divided dosage schedule.
- Titration: increase the total daily dosage in increments of 25 mg to 50 mg per day, if well-tolerated.
- Target dose: 300 mg to 450 mg per day, in divided doses, by the end of 2 weeks.
- Subsequent increases: increase in increments of 100 mg or less, once or twice weekly.
- Maximum daily dose: 900 mg (2.2).

Discontinuing Treatment

- Method of treatment discontinuation will vary depending on the patient's last ANC count:
- See package insert for appropriate ANC monitoring if abrupt treatment discontinuation is necessary because of severe neutropenia.
- Reduce the dose gradually over a period of 1 to 2 weeks if termination of clozapine therapy is planned and there is no evidence of moderate to severe neutropenia.
- For abrupt treatment discontinuation for a medical condition unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for general population patients until their ANC is ≥1500/μL and for BEN patients until their ANC is ≥1000/μL or above their baseline.
- Additional ANC monitoring is required for any patient reporting onset of fever (temperature of 38.5°C or 101.3°F or greater) during the 2 weeks after discontinuation.
- Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.

Re-Initiation of Treatment

- When restarting clozapine in patients who have discontinued clozapine (i.e., 2 days or more since the last dose), re-initiate with 12.5-mg once daily or twice daily. This is necessary to minimize the risk of hypotension, bradycardia, and syncope [see Warnings and Precautions (5.3).] If that dose is well tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment.

For additional safety information, please see full Prescribing Information, including Boxed WARNING, which can be found at www.clozapinerems.com.