**Indications**

**Treatment-Resistant Schizophrenia**
Clozapine tablets are indicated for the treatment of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with their use, Clozapine tablets should be used only in patients who have failed to respond adequately to standard antipsychotic treatment.

The effectiveness of Clozapine tablets in treatment-resistant schizophrenia was demonstrated in a 6-week, randomized, double-blind, active-controlled study comparing Clozapine tablets and chlorpromazine in patients who failed on other antipsychotics.

**Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders**
Clozapine is also indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history or recent clinical state. Suicidal behavior refers to actions by a patient that puts him/herself at risk for death.

The effectiveness of Clozapine in reducing the risk of recurrent suicidal behavior was demonstrated over a two-year treatment period in the InterSePT™ Trial.

**Important Safety Information**

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<th>BOXED WARNING: AGNULOCYTOSIS; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS</th>
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**AGNULOCYTOSIS:** Clozapine treatment has caused agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/mm³. Agranulocytosis can lead to serious infection and death. Prior to initiating treatment with Clozapine, obtain a baseline white blood cell count (WBC) and ANC. The ANC must be greater than or equal to 2000/mm³ and the WBC must be greater than or equal to 3500/mm³ for a patient to begin treatment with Clozapine. During treatment, patients must have regular monitoring of ANC and WBC. Discontinue Clozapine and do not rechallenge if the ANC is less than 1000/mm³ or the WBC is less than 2000/mm³. Advise patients to immediately report symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat). Because of the risk of agranulocytosis, Teva Clozapine is available only through a restricted program called the Teva Clozapine Patient Registry. Under the Teva Clozapine Patient Registry, prescribers, patients, and pharmacies must enroll in the program.

**ORTHOSTATIC HYPOTENSION, BRADYCARDIA, SYNCOPE:** Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with Clozapine treatment. The risk is highest during the initial titration period, particularly with rapid dose escalation. These reactions can occur with the first dose, with doses as low as 12.5 mg per day. Initiate treatment at 12.5 mg once or twice daily; titrate slowly; and use divided dosages. Use Clozapine cautiously in patients with cardiovascular or cerebrovascular disease or conditions predisposing to hypotension (e.g., dehydration, use of antihypertensive medications).

**SEIZURES:** Seizures have occurred with Clozapine treatment. The risk is dose-related. Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing. Use caution when administering Clozapine to patients with a history of seizures or other predisposing risk factors for seizure (CNS pathology, medications that lower the seizure threshold, alcohol abuse). Caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others.

**MYOCARDITIS AND CARDIOMYOPATHY:** Fatal myocarditis and cardiomyopathy have occurred with Clozapine treatment. Discontinue Clozapine and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with Clozapine-related myocarditis or cardiomyopathy should not be rechallenged with Clozapine. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur.

**INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS:** Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Clozapine is not approved for use in patients with dementia-related psychosis.

Clozapine tablets are contraindicated in patients with a history of Clozapine-induced agranulocytosis or severe granulocytopenia. Clozapine tablets are contraindicated in patients with previous hypersensitivity to Clozapine (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson syndrome) or any other component of Clozapine tablets.

Patients who are being treated with Clozapine must have a baseline WBC count and ANC before initiation of treatment, and a WBC count and ANC every week for the first 6 months. Thereafter, if acceptable WBC counts and ANCs (WBC count ≥3500/mm³ and ANC ≥2000/mm³) have been maintained during the first 6 months of continuous therapy, WBC counts and ANC can be monitored every 2 weeks for the next 6 months. Thereafter, if acceptable WBC counts and ANCs (WBC count...
Exercise caution when Clozapine is coadministered with other medications known to prolong the QTc interval. Discontinue arrhythmias, (e.g., syncope, presyncope, dizziness or palpitations), obtain a cardiac evaluation, and discontinue Clozapine. Eosinophilia, defined as a blood eosinophil count of greater than 700/mm³, has occurred with Clozapine treatment. In clinical trials, 1% of patients developed eosinophilia. Clozapine-related eosinophilia usually occurs during the first month of treatment and has been associated with myocarditis, pancreatitis, hepatitis, colitis and nephritis. If eosinophilia develops during Clozapine treatment, promptly evaluate for systemic reactions such as rash or other allergic symptoms, myocarditis, or other organ-specific disease associated with eosinophilia. If Clozapine-related systemic disease is suspected, discontinue Clozapine immediately.

Atypical antipsychotic drugs, including Clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycemia, dyslipidemia and body weight gain, and should be monitored at baseline and have periodic follow-up monitoring during treatment with Clozapine.

Pulmonary embolism and deep vein thrombosis have occurred in patients treated with Clozapine tablets. Consider the possibility of pulmonary embolism in patients who present with deep-vein thrombosis, acute dyspnea, chest pain or other respiratory signs and symptoms.

Clozapine has potent anticholinergic effects. Treatment with Clozapine can result in CNS and peripheral anticholinergic toxicity. Use with caution in the presence of narrow-angle glaucoma, concomitant anticholinergic medications, prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to serious adverse reactions. Clozapine treatment can cause fatal gastrointestinal adverse reactions such as constipation, intestinal obstruction, fecal impaction, and paralytic ileus. Constipation may be treated by ensuring adequate hydration and use of bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.
Clozapine can cause sedation and impairment of cognitive and motor performance. Caution patients about operating hazardous machinery, including automobiles, while they are taking Clozapine. These reactions may be dose-related and a reduction in dose may be required.

Tardive Dyskinesia has occurred in patients treated with antipsychotic drugs, including Clozapine. The syndrome consists of potentially irreversible, involuntary, dyskinetic movements. This may occur after relatively brief treatment with low doses, but more frequently and with greater severity at higher doses. Prescribe Clozapine in a manner that is most likely to minimize the risk of developing TD. Use the lowest effective dose for the shortest duration to control symptoms. Periodically assess the need for continued treatment. If signs and symptoms of tardive dyskinesia appear in a patient, drug discontinuation should be considered. However, some patients may require treatment with Clozapine despite the presence of the syndrome.

Patients taking benzodiazepines, antihypertensives, citalopram, caffeine, tobacco smoke, and inhibitors or inducers of the cytochrome P450 1A2, 2D6, and 3A4 isozyme systems, should be carefully monitored upon Clozapine initiation and during therapy. Because of initial sedation, the dose should be gradually escalated. Use caution when administering concomitant medications that prolong the QT interval or that induce or inhibit the metabolism of Clozapine. It may be necessary to reduce the Clozapine dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers. This does not represent all of the drug interactions that are possible with Clozapine. Please consult the full prescribing information for further information regarding drug interactions.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these infants. These complications have varied from self-limited to intensive care support and prolonged hospitalization. Clozapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The safety and effectiveness of Clozapine has not been established in pediatric patients. Because of the potential for serious adverse reactions in nursing infants from Clozapine, patients should discontinue nursing or Clozapine.

In the event of planned termination of Clozapine, reduce the dose gradually over 1 to 2 weeks. If abrupt discontinuation of Clozapine is necessary (e.g., because of agranulocytosis, leucopenia, or another medical condition), monitor carefully for the recurrence of psychotic symptoms and adverse reactions related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhea. Patients should be informed that if they miss taking Clozapine for more than 2 days, they should not restart their medication at the same dosage and should contact their physician for dosing instructions. They should re-initiate with 12.5 mg once or twice daily to minimize the risk of hypotension, bradycardia and syncope.

Phenylketonuric patients should be informed that Clozapine, USP Orally Disintegrating Tablets contain phenylalanine (a component of aspartame).

Commonly Observed Adverse Events observed in association with the use of Clozapine in clinical trials at an incidence of greater than 5% were: CNS reactions, including sedation, dizziness/vertigo, headache, and tremor; cardiovascular reactions, including tachycardia, hypotension; syncope autonomic nervous system reactions, including hypersalivation, sweating, dry mouth, and visual disturbances; gastrointestinal reactions, including constipation and nausea; and fever.

You may contact the Teva Clozapine Patient Registry at 1-800-507-8334 or visit www.Clozapineregistry.com.

Please see full Prescribing Information, including Boxed Warning, for additional important safety information.