

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CLOZAPINE ORALLY DISINTEGRATING TABLETS safely and effectively. See full prescribing information for CLOZAPINE ORALLY DISINTEGRATING TABLETS.

CLOZAPINE orally disintegrating tablets, for oral use
Initial U.S. Approval: 1989

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.

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. (2.1, 5.1)
Clozapine is available only through a restricted program called the Clozapine REMS. (5.2)

Orthostatic Hypotension, Bradycardia, and Syncope: Risk is dose-related. Starting with 12.5 mg, titrate gradually and use divided dosages. (2.2, 2.6, 5.3)
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. (2.2, 5.4)

Myocarditis and Cardiomyopathy: Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions. (5.5)
Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Clozapine is not approved for this condition. (5.6)

---RECENT MAJOR CHANGES---
Indications and Usage (1.1) 09/2015

Boxed Warning, Severe Neutropenia 09/2015
Dosage and Administration, Required Laboratory Testing, Prior to Initiation and During Therapy (2.1), Discontinuation of Treatment (2.5) 09/2015

Contraindications, History of Clozapine-Induced Agranulocytosis or Severe Granulocytopenia (4.1), Hypersensitivity (4.1) 09/2015
Warnings and Precautions, Severe Neutropenia (5.1), Clozapine REMS Program (5.2) 09/2015

---INDICATIONS AND USAGE---
Clozapine Orally Disintegrating Tablets are an atypical antipsychotic indicated for:
Treatment-resistant schizophrenia. Efficacy was established in an active-controlled study. (1.1, 14.1)
Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. Efficacy was established in an active-controlled study. (1.2, 14.2)

---DOSAGE AND ADMINISTRATION---
Starting Dose: 12.5 mg once daily or twice daily. (2.3)
Use cautious titration and divided dosage schedule. (2.5, 5.3)
Titration: increase the total daily dosage in increments of 25 mg to 50 mg per day, if well-tolerated. (2.3)
Target dose: 300 mg to 450 mg per day, in divided doses, by the end of 2 weeks. (2.3)
Subsequent increases: increase in increments of 100 mg or less, once or twice weekly. (2.3)



Rx only
Iss. 09/2015

CLOZAPINE ORALLY DISINTEGRATING TABLETS

5421
5422

Maximum daily dose: 900 mg (2.3)
Tablets rapidly disintegrate after placement in the mouth and may be chewed if desired. No water is needed (2.3).

---DOSAGE FORMS AND STRENGTHS---
Orally disintegrating tablets: 150 mg and 200 mg (3)

---CONTRAINDICATIONS---
Known hypersensitivity to clozapine or any other component of clozapine orally disintegrating tablets (4.1)

---WARNINGS AND PRECAUTIONS---
Eosinophilia: Assess for organ involvement (e.g., myocarditis, pancreatitis, hepatitis, colitis, nephritis). Discontinue if these occur. (5.7)
QT Interval Prolongation: Can be fatal. Consider additional risk factors for prolonged QT interval (disorders and drugs). (5.8)

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. Discontinue if these occur. (5.7)
OT Interval Prolongation: Can be fatal. Consider additional risk factors for prolonged QT interval (disorders and drugs). (5.8)

Neuroleptic Malignant Syndrome (NMS): Immediately discontinue and monitor closely. Assess for co-morbid conditions. (5.10)
Fever: Evaluate for infection and for neutropenia, NMS. (5.11)

Pulmonary Embolism (PE): Consider PE if respiratory distress, chest pain, or deep-vein thrombosis occur. (5.12)
Anticholinergic Toxicity: Use cautiously in presence of specific conditions (e.g., narrow angle glaucoma, use of anticholinergic drugs). (5.13)

Interference with Cognitive and Motor Performance: Advise caution when operating machinery, including automobiles. (5.14)
Weight Gain: Significant weight gain may occur. Monitor weight gain. (5.9)
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FULL PRESCRIBING INFORMATION
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Severe Neutropenia
Clozapine treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/ μ L. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with clozapine, a baseline ANC must be at least 1500/ μ L for the general population, and must be at least 1000/ μ L for patients with documented Benign Ectopic Neutropenia (BEN). During treatment, patients must have regular ANC monitoring. Advise patients to immediately report symptoms consistent with severe neutropenia or infection (e.g., fever, weakness, lethargy, or sore throat) [see Dosage and Administration (2.1), and Warnings and Precautions (5.1)].

Because of the risk of severe neutropenia, clozapine is available only through a restricted program under a Risk Evaluation Mitigation Strategy (REMS) called the Clozapine REMS Program [see Warnings and Precautions (5.2)].

Orthostatic Hypotension, Bradycardia, and 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) [see Dosage and Administration (2.3, and 2.6), and Warnings and Precautions (5.3)].

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 [see Dosage and Administration (2.3), Warnings and Precautions (5.4)].

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 [see Warnings and Precautions (5.5)].

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 [see Warnings and Precautions (5.6)].

1 INDICATIONS AND USAGE
1.1 Treatment-Resistant Schizophrenia
Clozapine Orally Disintegrating Tablets are indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. Because of the risks of severe neutropenia and seizure associated with their use, Clozapine Orally Disintegrating Tablets should be used only in patients who have failed to respond adequately to standard antipsychotic treatment [see Warnings and Precautions (5.1, 5.4)].

The effectiveness of Clozapine Orally Disintegrating Tablets in treatment-resistant schizophrenia was demonstrated in a 6-week, randomized, double-blind, active-controlled study comparing Clozapine Orally Disintegrating Tablets and chlorpromazine in patients who had failed other antipsychotics [see Clinical Studies (14)].

1.2 Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder
Clozapine Orally Disintegrating Tablets are 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 and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at risk for death.

The effectiveness of Clozapine Orally Disintegrating Tablets in reducing the risk of recurrent suicidal behavior was demonstrated over a two-year treatment period in the InterSePT™ trial [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION
2.1 Required Laboratory Testing Prior to Initiation and During Therapy
Prior to initiating treatment with clozapine orally disintegrating tablets, a baseline ANC must be obtained. The baseline ANC must be at least 1500/ μ L for the general population, and at least 1000/ μ L for patients with documented Benign Ectopic Neutropenia (BEN). To continue treatment, the ANC must be monitored regularly [see Warnings and Precautions (5.1)].

2.2 Important Administration Instructions
Clozapine orally disintegrating tablets should be immediately placed in the mouth after removing the tablet from the blister pack. Both the tablet and the contents should not be rechallenged with clozapine. The tablets can be allowed to disintegrate, or they may be chewed. They may be swallowed with saliva. No water is necessary for administration.

The orally disintegrating tablets in a blister pack should be left in the unopened blister until the time of use. Just prior to use, peel the foil from the blister and gently remove the orally disintegrating tablet. Do not push the tablets through the foil, because this could damage the tablet.

2.3 Titration
Starting with 12.5 mg once daily or twice daily. The total daily dose can be increased in increments of 25 mg to 50 mg per day, if well-tolerated, to achieve a target dose of 300 mg to 450 mg per day (administered in divided doses) by the end of 2 weeks. Subsequently, the dose can be increased once weekly or twice weekly, in increments of up to 100 mg. The maximum dose is 900 mg per day. Do not increase the total daily dose of clozapine more quickly than recommended for initial treatment.

2.4 Maintenance Treatment
Generally, patients responding to clozapine orally disintegrating tablets should continue maintenance treatment on their effective dose beyond the acute episode.

2.5 Discontinuation of Treatment
Method of treatment discontinuation will vary depending on the patient's last ANC:
• See Tables 2 or 3 for appropriate ANC monitoring based on the level of neutropenia if abrupt treatment discontinuation is necessary because of moderate to 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 clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for general population patients until their ANC is \geq 1500/ μ L and for BEN patients until their ANC is \geq 1000/ μ L 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 [see Warnings and Precautions (5.1)].

2.6 Re-Initiation of Treatment
When restarting clozapine orally disintegrating tablets in patients who have discontinued clozapine orally disintegrating tablets (i.e., 2 days or more since the last dose), re-initiate with 12.5 mg once daily or twice daily. This is necessary because of 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.

2.7 Dosage Adjustments with Concomitant use of CYP1A2, CYP2D6, CYP3A4 Inhibitors or CYP1A2, CYP3A4 Inducers
Dose adjustments may be necessary in patients with concomitant use of: strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin), moderate or weak CYP1A2 inhibitors (e.g., oral contraceptives, or caffeine); CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinine, duloxetine, terfenadine, or sertraline); CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John's wort, and rifampin); or CYP1A2 inducers (e.g., tobacco smoking) [Table 1] [see Drug Interactions (7)].

Table 1: Dose Adjustment in Patients Taking Concomitant Medications

Co-medication	Scenarios
Initializing clozapine orally disintegrating tablets while taking disintegrating tablets	Discontinuing a co-medication while continuing clozapine orally disintegrating tablets
Adding a co-medication while taking disintegrating tablets	Discontinuing a co-medication while taking disintegrating tablets
Adding a co-medication while taking disintegrating tablets	Discontinuing a co-medication while taking disintegrating tablets

2.8 Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers
It may be necessary to reduce the clozapine orally disintegrating tablets dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers [see Use in Specific Populations (8)].

3 DOSAGE FORMS AND STRENGTHS
Clozapine orally disintegrating tablets are available as 150 mg and 200 mg, round, yellow, orally disintegrating tablets.

4 CONTRAINDICATIONS
4.1 Hypersensitivity
Clozapine orally disintegrating tablets are contraindicated in patients with a history of serious hypersensitivity to clozapine (e.g., photosensitivity, vasculitis, rhabdomyolysis, or Stevens-Johnson Syndrome) or any other component of clozapine orally disintegrating tablets [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia

Background
Clozapine can cause neutropenia (a low absolute neutrophil count (ANC)), defined as a reduction below pre-treatment normal levels of blood neutrophils. The ANC is usually available as a component of the complete blood count (CBC), including differential, and is more relevant to drug-induced neutropenia than is the white blood cell (WBC) count. The ANC may also be calculated using the following formula: $ANC = \text{Total WBC count} \times \text{percentage of neutrophils}$. ANC is defined as the total percentage of neutrophils obtained from the differential (neutrophil "segs" plus neutrophil "bands"). Other granulocytes (eosinophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary [see Adverse Reactions (6.2)]. Neutropenia may be mild, moderate, or severe [see Tables 2 and 3]. To improve and standardize understanding, "severe neutropenia" replaces the previous terms severe leukopenia, severe granulocytopenia, or agranulocytosis.

Severe neutropenia, ANC less than ($<$) 500/ μ L, occurs in a small percentage of patients taking clozapine and is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks on treatment and then declines. The mechanism by which clozapine causes neutropenia is unknown and is not dose-dependent.

Two separate management algorithms are provided below, the first for patients in the general population, and the second for patients identified to have baseline neutropenia.

Clozapine Treatment and Monitoring in the General Patient Population [see Table 2]
Obtain a CBC, including the ANC value, prior to initiating treatment with clozapine to ensure the presence of a normal baseline neutrophil count (equal to or greater than 1500/ μ L) and to permit later comparisons. Patients in the general population with an ANC equal to or greater than (\geq) 1500/ μ L are considered within normal range [Table 2] and are eligible to initiate treatment. Weekly ANC monitoring is required for all patients during the first 6 months of treatment. If a patient's ANC remains equal to or greater than 1500/ μ L for the first 6 months of treatment, monitoring frequency may be reduced to every 2 weeks for the next 6 months. If the ANC remains equal to or greater than 1500/ μ L for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

Table 2: Clozapine Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring for the General Patient Population

ANC Level	Clozapine Treatment Recommendations	ANC Monitoring
Normal range (\geq 1500/ μ L)	• Initiate treatment • If treatment interrupted: $<$ 30 days, continue monitoring as before • $>$ 30 days, monitor as if new patient	• Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
Mild neutropenia (1000 to 1499/ μ L)	• Continue treatment	• Three times weekly until ANC \geq 1500/ μ L, then • Once ANC \geq 1500/ μ L, return to patient's last "Normal Range" ANC monitoring interval ²
Moderate neutropenia (500 to 999/ μ L)	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Resume treatment once ANC \geq 1000/ μ L	• Daily until ANC \geq 1000/ μ L, then • Three times weekly until ANC \geq 1500/ μ L, then • Once ANC \geq 1500/ μ L, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval ²
Severe Neutropenia (less than 500/ μ L)	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC \geq 1000/ μ L, then • Three times weekly until ANC \geq 1500/ μ L • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC \geq 1500/ μ L

1. Confirm all initial reports of ANC less than 1500/ μ L with a repeat ANC measurement within 24 hours.
2. If clinically appropriate

Clozapine Treatment and Monitoring in Patients with Benign Ectopic Neutropenia [see Table 3]
Benign ectopic neutropenia (BEN) is a condition observed in certain ethnic groups whose average ANC values are lower than "standard" laboratory ranges for neutrophils. It is most commonly observed in individuals of African descent (approximate prevalence of 25 to 50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin. BEN is more complex and heterogeneous than neutropenia, and is associated with a higher rate of myeloid maturation, are healthy, and do not suffer from repeated or severe infections. They are not at increased risk for developing clozapine-induced neutropenia. Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider hematology consultation before initiating or during clozapine treatment as necessary.

Patients with BEN require a different ANC algorithm for clozapine management due to their lower baseline ANC levels. Table 3 provides guidelines for managing clozapine treatment and ANC monitoring in patients with BEN.

Table 3: Patients with Benign Ectopic Neutropenia (BEN): Clozapine Treatment Recommendations Based on Absolute Neutrophil Count (ANC) Monitoring

ANC Level	Treatment Recommendations	ANC Monitoring
Normal BEN Range (Established ANC baseline \geq 1000/ μ L)	• Obtain at least two baseline ANC levels before initiating treatment • If treatment interrupted $<$ 30 days, continue monitoring as before • $>$ 30 days, monitor as if new patient	• Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
BEN Neutropenia (500 to 999/ μ L)	• Recommend hematology consultation • Continue treatment	• Three times weekly until ANC \geq 1000/ μ L or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval ²
BEN Severe Neutropenia (less than 500/ μ L)	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC \geq 500/ μ L, then • Three times weekly until ANC \geq patient's baseline • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC \geq 1000/ μ L or at patient's baseline

1. Confirm all initial reports of ANC less than 1500/ μ L with a repeat ANC measurement within 24 hours.
2. If clinically appropriate

General Guidelines for Management of All Patients with Fever or with Neutropenia
Fever: Interrupt clozapine as a precautionary measure in any patient who develops fever, defined as a temperature of 38.5°C (101.3°F) or greater, and obtain an ANC level. Fever is often the first sign of neutropenic infection.
• ANC less than 1000/ μ L: If fever occurs in any patient with an ANC less than 1000/ μ L, initiate appropriate workup and treatment for infection and refer to Tables 2 or 3 for management.
• Consider hematology consultation.
• See Neuroleptic Malignant Syndrome (NMS) and Fever under WARNINGS AND PRECAUTIONS (5) and Instructions for Patients, under PATIENT COUNSELING INFORMATION (17).

Rechallenge after an ANC less than 500/ μ L (severe neutropenia)
For some patients who experience severe clozapine-related neutropenia, the risk of serious psychiatric illness from discontinuing clozapine treatment may be greater than the risk of rechallenge (e.g. patients with severe schizophrenic illness who have no treatment options other than clozapine). A hematology consultation may be useful in deciding to rechallenge a patient. In general, however, do not rechallenge patients who develop severe neutropenia with clozapine orally disintegrating tablets or a clozapine product.

If a patient will be rechallenged, the clinician should consider thresholds provided in Tables 2 and 3, the patient's medical and psychiatric history, a discussion with the patient and his/her caregiver about the benefits and risks of clozapine rechallenge, and the severity and characteristics of the neutropenic episode.

Using Clozapine with Other Drugs Associated

- Eosinophilia *[see Warnings and Precautions (5.7)]*.
- QT Interval Prolongation *[see Warnings and Precautions (5.8)]*.
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) *[see Warnings and Precautions (5.9)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.10)]*.
- Fever *[see Warnings and Precautions (5.11)]*.
- Pulmonary Embolism *[see Warnings and Precautions (5.12)]*.
- Anticholinergic Toxicity *[see Warnings and Precautions (5.13)]*.
- Interference with Cognitive and Motor Performance *[see Warnings and Precautions (5.14)]*.
- Tardive Dyskinesia *[see Warnings and Precautions (5.15)]*.
- Patients with Phenyleketonuria *[see Warnings and Precautions (5.16)]*.
- Cerebrovascular Adverse Reactions *[see Warnings and Precautions (5.17)]*.
- Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation *[see Warnings and Precautions (5.18)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions (> 5% across clozapine clinical trials were: CNS reactions, including sedation, dizziness/vertigo, headache, and tremor; cardiovascular reactions, including tachycardia, hypertension, and syncope; autonomic nervous system reactions, including hypersalivation, sweating, dry mouth, and visual disturbances; gastrointestinal reactions, including constipation and nausea; and fever. Table 9 summarizes the most commonly reported adverse reactions (> 5%) in clozapine-treated patients (compared to chlorpromazine-treated patients) in the pivotal, 6-week, controlled trial in treatment-resistant schizophrenia.

Table 9: Common Adverse Reactions (> 5% in the 6-Week, Randomized, Chlorpromazine-Controlled Trial in Treatment-Resistant Schizophrenia

Adverse Reaction	Clozapine (N = 126) (%)	Chlorpromazine (N = 142) (%)
Sedation	21	13
Tachycardia	17	11
Constipation	16	12
Dizziness	14	16
Hypertension	13	38
Fever (hyperthermia)	13	4
Hypersalivation	13	1
Hypertension	12	5
Headache	10	10
Nausea/vomiting	10	12
Dry mouth	5	20

Table 10 summarizes the adverse reactions reported in clozapine-treated patients at a frequency of 2% or greater across all clozapine studies (excluding the 2 year InterSePT™ Study). These rates are not adjusted for duration of exposure.

Table 10: Adverse Reactions (> 2% Reported in Clozapine-treated Patients (N = 842) Across all Clozapine Studies (excluding the 2 year InterSePT™ Study)

Body System	Clozapine N = 842	Percentage of Patients
Adverse Reaction*		
Central Nervous System		
Drowsiness/Sedation	39	
Dizziness/Vertigo	19	
Headache	7	
Tremor	6	
Syncope	6	
Disturbed Sleep/Nightmares	4	
Restlessness	4	
Hypokinesia/Akinesia	4	
Agitation	4	
Seizures (convulsions)	3†	
Rigidity	3	
Akathisia	3	
Confusion	3	
Fatigue	2	
Insomnia	2	
Cardiovascular		
Tachycardia	25†	
Hypertension	9	
Hypertension	4	
Gastrointestinal		
Constipation	14	
Nausea	5	
Abdominal Discomfort/Heartburn	4	
Nausea/Vomiting	3	
Vomiting	3	
Diarrhea	2	
Urogenital		
Urinary abnormalities	2	
Autonomic Nervous System		
Salivation	31	
Sweating	6	
Dry mouth	6	
Visual disturbances	5	
Skin		
Rash	2	
Hemic/Lymphatic		
Leukopenia/Decreased WBC/Neutropenia	3	
Miscellaneous		
Fever	5	
Weight Gain	4	

†. Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

Table 11 summarizes the most commonly reported adverse reactions (> 10% of the clozapine or olanzapine group) in the InterSePT™ Study. This was an adequate and well-controlled, two-year study evaluating the efficacy of clozapine relative to olanzapine in reducing the risk of suicidal behavior in patients with schizophrenia or schizoaffective disorder. The rates are not adjusted for duration of exposure.

Table 11: Incidence of Adverse Reactions in Patients Treated with Clozapine or Olanzapine in the InterSePT™ Study (> 10% in the clozapine or olanzapine group)

Adverse Reactions	Clozapine N = 479 % Reporting	Olanzapine N = 477 % Reporting
Salivary hypersecretion	48%	6%
Somnolence	46%	25%
Weight increased	31%	56%
Dizziness (excluding vertigo)	27%	12%
Constipation	25%	10%
Insomnia	20%	33%
Nausea	17%	10%
Vomiting	17%	9%
Dyspepsia	14%	8%

Dystonia

Class effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity and at higher potencies and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of clozapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Central Nervous System

Delirium, EEG abnormal, myoclonus, paresthesia, possible cataplexy, status epilepticus, obsessive compulsive symptoms, and post-discontinuation cholinergic rebound adverse reactions.

Cardiovascular System

Atrial or ventricular fibrillation, ventricular tachycardia, QT interval prolongation, Torsades de Pointes, myocardial infarction, cardiac arrest, and periorbital edema.

Endocrine System

Pseudopheochromocytoma

Gastrointestinal System

Acute pancreatitis, dysphagia, salivary gland swelling.

Hepatobiliary System

Cholestasis, hepatitis, jaundice, hepatotoxicity, hepatic steatosis, hepatic necrosis, hepatic fibrosis, hepatic cirrhosis, liver injury (hepatic, cholestatic, and mixed), and liver failure.

Immune System Disorders

Angioedema, leukocytoclastic vasculitis.

Urogenital System

Acute interstitial nephritis, nocturnal enuresis, priapism, and renal failure.

Skin and Subcutaneous Tissue Disorders

Hypersensitivity reactions: photosensitvity, vasculitis, erythema multiforme, skin pigmentation disorder, and Stevens-Johnson Syndrome.

Musculoskeletal System and Connective Tissue Disorders

Myasthenic syndrome, rhabdomyolysis, and systemic lupus erythematosus.

Respiratory System

Aspiration, pleural effusion, pneumonia, lower respiratory tract infection.

Hemic and Lymphatic System

Mild, moderate, or severe leukopenia, agranulocytosis, granulocytopenia, WBC decreased, deep-ven thrombosis, elevated hemoglobin/hematocrit, erythrocyte sedimentation rate (ESR) increased, sepsis, thrombocytosis, and thrombocytopenia.

Vision Disorders

Narrow-angle glaucoma.

Miscellaneous

Creatine phosphokinase elevation, hyperuricemia, hyponatremia, and weight loss.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect Clozapine

Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP3A4, and CYP2D6. Use caution when administering clozapine orally disintegrating tablets concomitantly with drugs that are inducers or inhibitors of these enzymes.

CYP1A2 Inhibitors

Concomitant use of clozapine orally disintegrating tablets and CYP1A2 inhibitors can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the clozapine orally disintegrating tablets dose to one-third of the original dose when clozapine orally disintegrating tablets are coadministered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or enoxacin). The clozapine orally disintegrating tablets dose should be increased to the original dose when coadministration of strong CYP1A2 inhibitors is discontinued *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

Moderate or weak CYP1A2 inhibitors include oral contraceptives and caffeine. Monitor patients closely when clozapine orally disintegrating tablets are coadministered with these inhibitors. Consider reducing the clozapine orally disintegrating tablets dosage if necessary *[see Dosage and Administration (2.7)]*.

CYP2D6 and CYP3A4 Inhibitors

Concomitant treatment with clozapine orally disintegrating tablets and CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinidine, duloxetine, terbinafine, or sertraline) can increase clozapine levels and lead to adverse reactions *[see Clinical Pharmacology (12.3)]*. Use caution and monitor patients closely when using such inhibitors. Consider reducing the clozapine orally disintegrating tablets dose *[see Dosage and Administration (2.7)]*.

CYP1A2 and CYP3A4 Inducers

Concomitant treatment with drugs that induce CYP1A2 or CYP3A4 can decrease the plasma concentration of clozapine, resulting in decreased effectiveness of clozapine orally disintegrating tablets. Tobacco smoke is a moderate inducer of CYP1A2. Strong CYP3A4 inducers include carbamazepine, phenytoin, St. John’s wort, and rifampin. It may be necessary to increase the clozapine orally disintegrating tablets dose if used concomitantly with inducers of these enzymes. However, concomitant use of clozapine orally disintegrating tablets and strong CYP3A4 inducers is not recommended *[see Dosage and Administration (2.7)]*.

Consider reducing the clozapine orally disintegrating tablets dosage when discontinuing coadministered enzyme inducers; because discontinuation of inducers can result in increased clozapine plasma levels and an increased risk of adverse reactions *[see Dosage and Administration (2.7)]*.

Drugs that Cause QT Interval Prolongation

Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of clozapine. Drugs that cause QT prolongation include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, and pimozide), specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin), Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, propofol or tacrolimus) *[see Warnings and Precautions (5.8)]*.

7.2 Potential for Clozapine to Affect Other Drugs

Concomitant use of clozapine with other drugs metabolized by CYP2D6 can increase levels of these CYP2D6 substrates. Use caution when coadministering clozapine with other drugs that are metabolized by CYP2D6. It may be necessary to use lower doses of such drugs than usually prescribed. Such drugs include specific antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

Risk Summary

There are no adequate or well-controlled studies of clozapine in pregnant women.

Reproduction studies have been performed in rats and rabbits at doses up to 0.4 and 0.9 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m² body surface area basis. The studies revealed no evidence of impaired fertility or harm to the fetus due to clozapine. Because animal reproduction studies are not always predictive of human response, clozapine orally disintegrating tablets should be used during pregnancy only if clearly needed.

Clinical Considerations

Consider the risk of exacerbation of psychosis when discontinuing or changing treatment with antipsychotic medications during pregnancy and postpartum. Consider early screening for gestational diabetes for patients treated with antipsychotic medications *[see Warnings and Precautions (5.9)]*. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Monitor neonates for symptoms of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding difficulties. The severity of complications can vary from self-limited symptoms to some neonates requiring intensive care unit support and prolonged hospitalization.

Animal Data

In embryofetal developmental studies, clozapine had no effects on maternal parameters, litter sizes, or fetal parameters when administered orally to pregnant rats and rabbits during the period of organogenesis at doses up to 0.4 and 0.9 times, respectively, the MRHD of 900 mg/day on a mg/m² body surface area basis.

In perinatal/postnatal developmental studies, pregnant female rats were administered clozapine over the last third of pregnancy and until day 21 postpartum. Observations were made on fetuses at birth and during the postnatal period; the offspring were allowed to reach sexual maturity and mated. Clozapine caused a decrease in maternal body weight but had no effects on litter size or body weights of either the F1 or F2 generations at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m² body surface area basis.

8.3 Nursing Mothers

Clozapine is present in human milk. Because of the potential for serious adverse reactions in nursing infants from clozapine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients in clinical studies utilizing clozapine to determine whether those over 65 years of age differ from younger subjects in their response to clozapine.

Orthostatic hypotension and tachycardia can occur with clozapine treatment *[see Boxed Warning and Warnings and Precautions (5.3)]*. Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation *[see Warnings and Precautions (5.13)]*.

Carefully select clozapine doses in elderly patients, taking into consideration their greater frequency of decreased hepatic, renal, or cardiac function, as well as other concomitant disease and other drug therapy. Clinical experience suggests that the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women *[see Warnings and Precautions (5.15)]*.

8.6 Patients with Renal or Hepatic Impairment

Dose reduction may be necessary in patients with significant impairment of renal or hepatic function. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted *[see Dosage and Administration (2.8), Clinical Pharmacology (12.3)]*.

8.7 CYP2D6 Poor Metabolizers

Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted *[see Dosage and Administration (2.8), Clinical Pharmacology (12.3)]*.

8.8 Hospice Patients

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of 6 months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychiatric symptoms and the patient’s terminal illness.

10 OVERDOSAGE

10.1 Overdose Experience

The most commonly reported signs and symptoms associated with clozapine overdose are: sedation, delirium, coma, tachycardia, hypotension, respiratory depression or failure, and hypersalivation. There are reports of aspiration pneumonia, cardiac arrhythmias, and seizure. Fatal overdoses have been reported with clozapine, generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g.

10.2 Management of Overdosage

For the most up-to-date information on the management of clozapine overdose, contact a certified Regional Poison Control Center (1-800-222-1222). Telephone numbers of certified Regional Poison Control Centers are listed in the *Physicians’ Desk Reference*®, a registered trademark of PDR Network. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Monitor cardiac status and vital signs. Use general symptomatic and supportive measures. There are no specific antidotes for clozapine.

In managing overdose, consider the possibility of multiple-drug involvement.

11 DESCRIPTION

Clozapine Orally Disintegrating Tablets, an atypical antipsychotic drug, are a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo [b,e] [1,4] diazepine. The structural formula is:



Each orally disintegrating tablet contains clozapine, USP equivalent to 150 mg and 200 mg.

The active component of Clozapine Orally Disintegrating Tablets is clozapine, USP. The remaining components are aspartame powder, colloidal silicon dioxide, croscopollose, magnesium stearate, mannitol, microcrystalline cellulose, peppermint flavor, sodium stearyl fumarate and xylitol.

THIS PRODUCT CONTAINS ASPARTAME AND IS NOT INTENDED FOR USE BY INFANTS. PHENYLKETONURICS: CONTAINS PHENYLALANINE *[see Warnings and Precautions (5.16)]*. Phenylalanine is a component of aspartame. Each 150 mg, orally disintegrating tablet contains 30 mg aspartame, thus, 16.8 mg phenylalanine. Each 200 mg, orally disintegrating tablet contains 40 mg aspartame, thus, 22.4 mg phenylalanine. The allowable daily intake of aspartame is 50 mg per kilogram of body weight per day.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of clozapine is unknown. However, it has been proposed that the therapeutic efficacy of clozapine in schizophrenia is mediated through antagonism of the dopamine 2 (D₂) and the serotonin type 2A (5-HT_{2A}) receptors. Clozapine orally disintegrating tablets also act as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors.

12.2 Pharmacodynamics

Clozapine demonstrated binding affinity to the following receptors: histamine H₁ (K_i 1.1 nM), adrenergic α_{1A} (K_i 1.6 nM), serotonin 5-HT_{1A} (K_i 4 nM), serotonin 5-HT_{2A} (K_i 5.4 nM), muscarinic M₁ (K_i 6.2 nM), serotonin 5-HT₇ (K_i 6.3 nM), serotonin 5-HT_{2C} (K_i 9.4 nM), dopamine D₄ (K_i 24 nM), adrenergic α_{2A} (K_i 90 nM), serotonin 5-HT₃ (K_i 95 nM), serotonin 5-HT_{1A} (K_i 120 nM), dopamine D₂ (K_i 160 nM), dopamine D₁ (K_i 270 nM), dopamine D₅ (K_i 454 nM), and dopamine D₃ (K_i 555 nM). Clozapine causes little or no prolactin elevation.

Clinical electroencephalogram (EEG) studies demonstrated that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs. Sharp wave activity and spike and wave complexes may also develop. Patients have reported an intensification of dream activity during clozapine therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

12.3 Pharmacokinetics

Absorption

In man, clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Clozapine orally disintegrating tablets are bioequivalent to Clozarin® (clozapine) tablets, a registered trademark of Novartis Pharmaceuticals Corporation. Following a dosage of 100 mg b.i.d., the average steady-state peak plasma concentration was 413 ng/mL (range: 132 to 854 ng/mL), occurring at the average of 2.3 hours (range: 1 to 6 hours) after dosing. The average minimum concentration at steady-state was 168 ng/mL (range: 45 to 574 ng/mL), after 100 mg b.i.d. dosing.

A comparative bioequivalence/bioavailability study was conducted in 32 patients (with schizophrenia or schizoaffective disorder) comparing clozapine orally disintegrating 200 mg tablets to 2 x clozapine orally disintegrating 100 mg tablets (the approved reference product) under fasted conditions. The study also evaluated the effect of food and chewing on the pharmacokinetics of the 200 mg tablet. Under fasted conditions, the mean AUC_{0-∞} and C_{max,ss} of clozapine for the 200 mg tablets were equivalent to those of the 2 x 100 mg tablets. The mean C_{max,ss} of clozapine for clozapine orally disintegrating 200 mg tablets was 85% that for 2 x 100 mg clozapine orally disintegrating tablets. This decrease in C_{max,ss} for clozapine orally disintegrating 200 mg tablets is not clinically significant.

For clozapine orally disintegrating 200 mg tablets, food significantly increased the C_{min,ss} of clozapine by 21%. However, this increase is not clinically significant. The mean AUC_{0-∞} and the mean AUC of clozapine under fed conditions were equivalent to those under fasted conditions. Food delayed clozapine absorption by 1.5 hours, from a median T_{max} of 2.5 hours under fasted conditions to 4 hours under fed conditions.

The mean C_{max,ss} of clozapine under chewed conditions for clozapine orally disintegrating 200 mg tablets was about 86% that for 2 x 100 mg clozapine orally disintegrating tablets under non-chewed conditions, while the AUC_{0-∞} and C_{min,ss} values were similar between the chewed and non-chewed conditions.

In a food-effect study, a single dose of clozapine orally disintegrating tablets 12.5 mg was administered to healthy volunteers under fasting conditions and after a high-fat meal. When clozapine orally disintegrating tablets were administered after a high-fat meal, the C_{max} of both clozapine and its active metabolite, desmethylclozapine, were decreased by approximately 20%, compared to administration under fasting conditions, while the AUC values were unchanged. This decrease in C_{max} is not clinically significant. Therefore, clozapine orally disintegrating tablets can be taken without regard to meals.

Distribution

Clozapine is approximately 97% bound to serum proteins. The interaction between clozapine and other highly protein-bound drugs has not been fully evaluated but may be important *[see Drug Interactions (7)]*.

Metabolism and Excretion

Clozapine is almost completely metabol