Clozapine Orodispersible tablet
Alkepin ODT

1. NAME OF THE MEDICINAL PRODUCT: Clozapine Orodispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Alkepin ODT 12.5
Each uncoated Orodispersible tablet contains:
Clozapine IP …… 12.5 mg

Alkepin ODT 25
Each uncoated Orodispersible tablet contains:
Clozapine IP ……..…… 25 mg

Alkepin ODT 50
Each uncoated Orodispersible tablet contains:
Clozapine IP ……...…… 50 mg

Alkepin ODT 100
Each uncoated Orodispersible tablet contains:
Clozapine IP ……..…… 100 mg

Alkepin ODT 200
Each uncoated Orodispersible tablet contains:
Clozapine IP ……..…… 200 mg

3. PHARMACEUTICAL FORM
Orodispersible tablet (ODT)

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of schizophrenia
Clozapine ODT is indicated in the management of schizophrenic patients.

Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder
Clozapine ODT is 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.

4.2 Posology and Method of Administration

Required Laboratory Testing Prior to Initiation and During Therapy:
Prior to initiating treatment with Clozapine ODT, a baseline ANC (absolute neutrophil count) 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.

Important Administration Instructions:
Clozapine ODT should be immediately placed in the mouth after removing the tablet from the blister pack. The tablet disperse rapidly by contact with saliva after placement in the mouth. The tablets can be allowed to disintegrate and they may be swallowed with saliva or with boiled and cooled water or they may disperse the tablet in water and take.

The orodispersible 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 orodispersible tablet. Do not push the tablets through the foil, because this could damage the tablet.

Dosing Information:
The starting dose is 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. To minimize the risk of orthostatic hypotension, bradycardia, and syncope, it is necessary to use this low starting dose, gradual titration schedule, and divided dosages.

Clozapine ODT can be taken with or without food.

Maintenance Treatment:
Generally, patients responding to Clozapine ODT should continue maintenance treatment on their effective dose beyond the acute episode.

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 ODT 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 ≥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 ODT in patients who have discontinued Clozapine ODT (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. If that dose is well-tolerated, the dose may be increased to the previously therapeutic dose more quickly than recommended for initial treatment.

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, or enoxacin); moderate or weak CYP1A2 inhibitors (e.g., oral contraceptives, or caffeine); CYP2D6 or CYP3A4 inhibitors (e.g., cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinidine, duloxetine, terbinafine, or sertraline); CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John's wort, and rifampin); or CYP1A2 inducers (e.g., tobacco smoking).

Table 1: Dose Adjustment in Patients Taking Concomitant Medications

Co-medication	**Scenarios**		
	Initiating Clozapine ODT while taking a co-medication	Adding a co-medication while taking Clozapine ODT	Discontinuing a co-medication while continuing Clozapine ODT
Strong CYP1A2 Inhibitors	Use one third of the Clozapine ODT dose.		Increase Clozapine ODT dose based on clinical response.
Moderate or Weak CYP1A2 Inhibitors	Monitor for adverse reactions. Consider reducing the Clozapine ODT dose if necessary		Monitor for lack of effectiveness. Consider increasing Clozapine ODT dose if necessary.
CYP2D6 or CYP3A4 Inhibitors			
Strong CYP3A4 Inducers	Concomitant use is not recommended. However, if the inducer is necessary, it may be necessary to increase the Clozapine ODT dose. Monitor for decreased effectiveness.		Reduce Clozapine ODT dose based on clinical response
Moderate or Weak CYP1A2 or CYP3A4 Inducers	Monitor for decreased effectiveness. Consider increasing the Clozapine ODT dose if necessary.		Monitor for adverse reactions. Consider reducing the Clozapine ODT dose if necessary

Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers
It may be necessary to reduce the Clozapine ODT dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

Orthostatic hypotension and tachycardia can occur with clozapine treatment. 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.

Carefully select Clozapine ODT 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.

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.

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.

4.3 Contraindications:
Hypersensitivity
Clozapine ODT is contraindicated in patients with a history of serious hypersensitivity to clozapine (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens - Johnson syndrome) or any other component of Clozapine ODT

4.4 Special Warnings and Special Precautions for Use:

Severe Neutropenia
Background
Clozapine ODT 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 equals the Total WBC count multiplied by the total percentage of neutrophils obtained from the differential (neutrophil "segs" plus neutrophil "bands").* Other granulocytes (basophils and eosinophils) contribute minimally to neutropenia and their measurement is not necessary. 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/μL, occurs in a small percentage of patients taking Clozapine ODT 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 ODT 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 ODT Treatment and Monitoring in the General Patient Population (see Table 2)
Obtain a CBC, including the ANC value, prior to initiating treatment with Clozapine ODT to ensure the presence of a normal baseline neutrophil count (equal to or greater than 1500/μL) and to permit later comparisons. Patients in the general population with an ANC equal to or greater than (≥)1500/μL 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/μL 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/μL for the second 6 months of continuous therapy, ANC monitoring frequency may be reduced to once every 4 weeks thereafter.

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

ANC Level	Clozapine ODT Treatment Recommendations	ANC Monitoring

Normal range (≥1500/μL)	• 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

	Discontinuation for reasons other than neutropenia	See maintenance treatment
Mild Neutropenia (1000 to 1499/μL)*	• Continue treatment	• Three times weekly until ANC ≥1500/μL • Once ANC ≥1500/μL, return to patient's last "Normal Range" ANC monitoring interval**
Moderate neutropenia (500 to 999/μL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Resume treatment once ANC ≥1000/μL	• Daily until ANC ≥1000/μL, then • Three times weekly until ANC ≥1500/μL • Once ANC ≥1500/μL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**
Severe Neutropenia (less than 500/μL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥1000/μL, then • Three times weekly until ANC ≥1500/μL • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1500/μL

* Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 hours
** If clinically appropriate

Clozapine ODT Treatment and Monitoring in Patients with Benign Ethnic Neutropenia (see Table 3)

Benign ethnic 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 25-50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin. BEN is more common in men. Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections. They are not at increased risk for developing Clozapine ODT-induced neutropenia. Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider hematology consultation before initiating or during Clozapine ODT treatment as necessary.

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

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

ANC Level	Treatment Recommendations	ANC Monitoring

Normal BEN Range (Established ANC baseline ≥1000/µL)	• 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

	• Discontinuation of treatment for reasons other than neutropenia	• See Maintenance treatment
BEN Neutropenia (500 to 999/µL)*	• Recommend hematology consultation • Continue treatment	• Three times weekly until ANC ≥ 1000/µL or ≥ patient's known baseline • Once ANC ≥ 1000/µL or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval.**
BEN Severe Neutropenia (less than 500/µL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Do not rechallenge	• Daily until ANC ≥500/µL, then • Three times weekly until ANC ≥ patient's baseline • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/µL or at patient's

* Confirm all initial reports of ANC less than 1500/µL with a repeat ANC measurement within 24 hours
** If clinically appropriate

General Guidelines for Management of All Patients with Fever or with Neutropenia

- Fever: Interrupt Clozapine ODT 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/µL: If fever occurs in any patient with an ANC less than 1000/µL, 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

Rechallenge after an ANC less than 500/µL (severe neutropenia)

For some patients who experience severe Clozapine ODT-related neutropenia, the risk of serious psychiatric illness from discontinuing Clozapine ODT treatment may be greater than the risk of rechallenge (e.g., patients with severe schizophrenic illness who have no treatment options other than Clozapine ODT). 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 ODT 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 ODT rechallenge, and the severity and characteristics of the neutropenic episode.

Using Clozapine ODT with Other Drugs Associated with Neutropenia

It is unclear if concurrent use of other drugs known to cause neutropenia increases the risk or severity of Clozapine ODT-induced neutropenia. There is no strong scientific rationale to avoid Clozapine ODT treatment in patients concurrently treated with these drugs. If Clozapine ODT is used concurrently with an agent known to cause neutropenia (e.g., some chemotherapeutic agents), consider monitoring patients more closely than the treatment guidelines provided in Tables 2 and 3. Consult with the treating oncologist in patients receiving concomitant chemotherapy.

Orthostatic Hypotension, Bradycardia, and Syncope

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, at doses as low as 12.5 mg. These reactions can be fatal. The syndrome is consistent with neurally mediated reflex bradycardia (NMRB).

Treatment must begin at a maximum dose of 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 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 weekly or twice weekly, in increments of up to 100 mg. The maximum dose is 900 mg per day. Use cautious titration and a divided dosage schedule to minimize the risk of serious cardiovascular reactions *[see Dosage and Administration]*. Consider reducing the dose if hypotension occurs. When restarting patients who have had even a brief interval off Clozapine ODT (i.e., 2 days or more since the last dose), re-initiate treatment at 12.5 mg once daily or twice daily *[see Dosage and Administration]*

Use Clozapine ODT cautiously in patients with cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (e.g., concomitant use of antihypertensives, dehydration and hypovolemia).

Seizures

Seizure has been estimated to occur in association with clozapine use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). The risk of seizure is dose-related. Initiate treatment with a low dose (12.5 mg), titrate slowly, and use divided dosing.

Use caution when administering Clozapine ODT to patients with a history of seizures or other predisposing risk factors for seizure (e.g., head trauma or other CNS pathology, use of medications that lower the seizure threshold, or alcohol abuse). Because of the substantial risk of seizure associated with Clozapine ODT use, caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others (e.g., driving an automobile, operating complex machinery, swimming, climbing).

Myocarditis and Cardiomyopathy

Myocarditis and cardiomyopathy have occurred with the use of clozapine. These reactions can be fatal. Discontinue Clozapine ODT and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with Clozapine ODT. However, if the benefit of Clozapine ODT treatment is judged to outweigh the potential risks of recurrent myocarditis or cardiomyopathy, the clinician may consider rechallenge with Clozapine ODT in consultation with a cardiologist, after a complete cardiac evaluation, and under close monitoring.

Consider the possibility of myocarditis or cardiomyopathy in patients receiving Clozapine ODT who present with chest pain, dyspnea, persistent tachycardia at rest, palpitations, fever, flu-like symptoms, hypotension, other signs or symptoms of heart failure, or electrocardiographic findings (low voltages, ST-T abnormalities, arrhythmias, right axis deviation, and poor R wave progression). Myocarditis most frequently presents within the first two months of clozapine treatment. Symptoms of cardiomyopathy generally occur later than clozapine-associated myocarditis and usually after 8 weeks of treatment. However, myocarditis and cardiomyopathy can occur at any period during treatment with Clozapine ODT. It is common for nonspecific flu-like symptoms such as malaise, myalgia, pleuritic chest pain, and low-grade fevers to precede more overt signs of heart failure. Typical laboratory findings include elevated troponin I or T, elevated creatinine kinase-MB, peripheral eosinophilia, and elevated C-reactive protein (CRP). Chest roentgenogram may demonstrate cardiac silhouette enlargement, and cardiac imaging (echocardiogram, radionucleotide studies, or cardiac catheterization) may reveal evidence of left ventricular dysfunction.

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. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality in this population. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Clozapine ODT is not approved for the treatment of patients with dementia-related psychosis.

Eosinophilia
Eosinophilia, defined as a blood eosinophil count of greater than 700/μL, has occurred with clozapine treatment. In clinical trials, approximately 1% of patients developed eosinophilia. Clozapine-related eosinophilia usually occurs during the first month of treatment. In some patients, it has been associated with myocarditis, pancreatitis, hepatitis, colitis, and nephritis. Such organ involvement could be consistent with a drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), also known as drug induced hypersensitivity syndrome (DIHS).

If eosinophilia develops during Clozapine ODT treatment, evaluate promptly for signs and symptoms of 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 ODT immediately.
If a cause of eosinophilia unrelated to clozapine is identified (e.g., asthma, allergies, collagen vascular disease, parasitic infections, and specific neoplasms), treat the underlying cause and continue Clozapine ODT.

Clozapine-related eosinophilia has also occurred in the absence of organ involvement and can resolve without intervention. There are reports of successful rechallenge after discontinuation of clozapine, without recurrence of eosinophilia. In the absence of organ involvement, continue Clozapine ODT under careful monitoring. If the total eosinophil count continues to increase over several weeks in the absence of systemic disease, the decision to interrupt Clozapine ODT therapy and rechallenge after the eosinophil count decreases should be based on the overall clinical assessment, in consultation with an internist or hematologist.

QT Interval Prolongation
QT prolongation, Torsades de Pointes and other life-threatening ventricular arrhythmias, cardiac arrest, and sudden death have occurred with clozapine treatment. When prescribing Clozapine ODT, consider the presence

of additional risk factors for QT prolongation and serious cardiovascular reactions. Conditions that increase these risks include the following: history of QT prolongation, long QT syndrome, family history of long QT syndrome or sudden cardiac death, significant cardiac arrhythmia, recent myocardial infarction, uncompensated heart failure, treatment with other medications that cause QT prolongation, treatment with medications that inhibit the metabolism of Clozapine ODT, and electrolyte abnormalities.

Prior to initiating treatment with Clozapine ODT, perform a careful physical examination, medical history, and concomitant medication history. Consider obtaining a baseline ECG and serum chemistry panel. Correct electrolyte abnormalities. Discontinue Clozapine ODT if the QTc interval exceeds 500 msec. If patients experience symptoms consistent with Torsades de Pointes or other arrhythmias (e.g., syncope, presyncope, dizziness, or palpitations), obtain a cardiac evaluation and discontinue Clozapine ODT.

Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of Clozapine ODT. Drugs that cause QT prolongation include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide), specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin), Class 1A antiarrhythmic medications (e.g., quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus). Clozapine ODT is primarily metabolized by CYP isoenzymes 1A2, 2D6, and 3A4. Concomitant treatment with inhibitors of these enzymes can increase the concentration of Clozapine ODT.

Hypokalemia and hypomagnesemia increase the risk of QT prolongation. Hypokalemia can result from diuretic therapy, diarrhea, and other causes. Use caution when treating patients at risk for significant electrolyte disturbance, particularly hypokalemia. Obtain baseline measurements of serum potassium and magnesium levels, and periodically monitor electrolytes. Correct electrolyte abnormalities before initiating treatment with Clozapine ODT.

Metabolic Changes
Atypical antipsychotic drugs, including Clozapine ODT, have been associated with metabolic changes that can increase cardiovascular and cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Clozapine ODT. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on Clozapine ODT should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has

resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia
Undesirable alterations in lipids have occurred in patients treated with atypical antipsychotics, including Clozapine ODT. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using Clozapine ODT, is recommended.

Weight Gain
Weight gain has occurred with the use of antipsychotics, including Clozapine ODT. Monitor weight during treatment with Clozapine ODT.

Neuroleptic Malignant Syndrome
Antipsychotic drugs including Clozapine ODT can cause a potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Associated findings can include elevated creatine phosphokinase (CPK), myoglobinuria, rhabdomyolysis, and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to consider the presence of other serious medical conditions (e.g., severe neutropenia, infection, heat stroke, primary CNS pathology, central anticholinergic toxicity, extrapyramidal symptoms, and drug fever).

The management of NMS should include (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of co-morbid medical conditions. There is no general agreement about specific pharmacological treatments for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. NMS can recur. Monitor closely if restarting treatment with antipsychotics.

NMS has occurred with clozapine monotherapy and with concomitant CNS-active medications, including lithium.

Fever
During clozapine therapy, patients have experienced transient, clozapine-related fever. The peak incidence is within the first 3 weeks of treatment. While this fever is generally benign and self- limited, it may necessitate discontinuing treatment. The fever can be associated with an increase or decrease in WBC count. Carefully evaluate patients with fever to rule out severe neutropenia or infection. Consider the possibility of NMS.

Pulmonary Embolism
Pulmonary embolism and deep vein thrombosis have occurred in patients treated with clozapine. Consider the possibility of pulmonary embolism in patients who present with deep vein thrombosis, acute dyspnea, chest pain, or with other respiratory signs and symptoms. Whether pulmonary embolus and deep vein thrombosis can be attributed to clozapine or some characteristic(s) of patients is not clear.

Anticholinergic Toxicity
Clozapine ODT has potent anticholinergic effects. Treatment with Clozapine ODT 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 significant adverse reactions.

Treatment with Clozapine ODT can result in gastrointestinal adverse reactions, including constipation, intestinal obstruction, fecal impaction, and paralytic ileus. Such reactions can be fatal. Constipation should be initially treated by ensuring adequate hydration and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Interference with Cognitive and Motor Performance
Clozapine ODT can cause sedation and impairment of cognitive and motor performance. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that Clozapine ODT does not affect them adversely. These reactions may be dose-related. Consider reducing the dose if they occur.

Tardive Dyskinesia
Tardive dyskinesia (TD) has occurred in patients treated with antipsychotic drugs, including Clozapine ODT. The syndrome consists of potentially irreversible, involuntary, dyskinetic movements. The risk of TD and the likelihood that it will become irreversible are believed to increase with greater durations of treatment and higher total cumulative doses. However, the syndrome can develop after relatively brief treatment periods at low doses. Prescribe Clozapine ODT in a manner that is most likely to minimize the risk of developing TD. Use the lowest effective dose and the shortest duration necessary to control symptoms. Periodically assess the need for continued treatment. Consider discontinuing treatment if TD occurs. However, some patients may require treatment with Clozapine ODT despite the presence of the syndrome.

There is no known treatment for TD. However, the syndrome may remit partially or completely if treatment is discontinued. Antipsychotic treatment, itself, may suppress (or partially suppress) the signs and symptoms, and it has the potential to mask the underlying process. The effect of symptom suppression on the long-term course of TD is unknown.

Cerebrovascular Adverse Reactions
In controlled trials, elderly patients with dementia-related psychosis treated with some atypical antipsychotics had an increased risk (compared to placebo) of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities. The mechanism for this increased risk is not known. An increased risk cannot be excluded for Clozapine ODT or other antipsychotics or other patient populations. Clozapine ODT should be used with caution in patients with risk factors for cerebrovascular adverse reactions.

Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation of Clozapine ODT
If abrupt discontinuation of Clozapine ODT is necessary (because of severe neutropenia or another medical condition, for example), monitor carefully for the recurrence of psychotic symptoms and adverse reactions related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting, and diarrhea.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Potential for Other Drugs to Affect Clozapine ODT
Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP3A4, and CYP2D6. Use caution when administering Clozapine ODT concomitantly with drugs that are inducers or inhibitors of these enzymes.

CYP1A2 Inhibitors
Concomitant use of Clozapine ODT and CYP1A2 inhibitors can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the Clozapine ODT dose to one third of the original dose when Clozapine ODT is coadministered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or

enoxacin). The Clozapine ODT dose should be increased to the original dose when coadministration of strong CYP1A2 inhibitors is discontinued.

Moderate or weak CYP1A2 inhibitors include oral contraceptives and caffeine. Monitor patients closely when Clozapine ODT is coadministered with these inhibitors. Consider reducing the Clozapine ODT dosage if necessary.

CYP2D6 and CYP3A4 Inhibitors
Concomitant treatment with Clozapine ODT 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. Use caution and monitor patients closely when using such inhibitors. Consider reducing the Clozapine ODT dose.

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 ODT. 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 ODT dose if used concomitantly with inducers of these enzymes. However, concomitant use of Clozapine ODT and strong CYP3A4 inducers is not recommended.

Consider reducing the Clozapine ODT dosage when discontinuing coadministered enzyme inducers, because discontinuation of inducers can result in increased clozapine plasma levels and an increased risk of adverse reactions.

Drugs that Cause QT Interval Prolongation
Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of Clozapine ODT. 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, probucol or tacrolimus).

Potential for Clozapine ODT to Affect Other Drugs
Concomitant use of Clozapine ODT with other drugs metabolized by CYP2D6 can increase levels of these CYP2D6 substrates. Use caution when coadministering Clozapine ODT 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).

4.6 Fertility, Pregnancy and Lactation
Pregnancy
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/m^2 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 ODT 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. 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.

Nursing Mothers
Clozapine ODT is present in human milk. Because of the potential for serious adverse reactions in nursing infants from Clozapine ODT, 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.

4.7 Effects on Ability to Drive and Use Machines
Because Clozapine ODT may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Clozapine ODT therapy does not affect them adversely.

4.8 Undesirable Effects
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Severe Neutropenia
- Orthostatic Hypotension, Bradycardia, and Syncope
- Seizures
- Myocarditis and Cardiomyopathy
- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Eosinophilia
- QT Interval Prolongation
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)
- Neuroleptic Malignant Syndrome
- Fever
- Pulmonary Embolism
- Anticholinergic Toxicity
- Interference with Cognitive and Motor Performance
- Tardive Dyskinesia
- Cerebrovascular Adverse Reactions
- Recurrence of Psychosis and Cholinergic Rebound after Abrupt Discontinuation

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, hypotension, and syncope; autonomic nervous system reactions, including hypersalivation, sweating, dry mouth, and visual disturbances; gastrointestinal reactions, including constipation and nausea; and fever.

Common Adverse Reactions (≥5%) in the 6-Week, Randomized, Chlorpromazine controlled Trial in Treatment-Resistant Schizophrenia
Sedation, tachycardia, constipation, dizziness, hypotension, fever (hyperthermia), hypersalivation, hypertension, headache, nausea/vomiting, dry mouth.

Adverse Reactions (≥2%) Reported in Clozapine-treated Patients (N=842) across all Clozapine Studies
Central nervous system: drowsiness/sedation, dizziness/vertigo, headache, tremor, syncope, disturbed sleep/nightmares, restlessness, hypokinesia/ akinesia, agitation, seizures (convulsions), rigidity, akathisia, confusion, fatigue, insomnia

Cardiovascular: Tachycardia, hypotension, hypertension

Gastrointestinal: constipation, nausea, abdominal discomfort/heartburn, nausea/vomiting, vomiting, diarrhea

Urogenital: urinary abnormalities

Autonomic nervous system: salivation, sweating, dry mouth, visual disturbances

Skin: Rash

Hemic/ Lymphatic: Leukopenia/ decreased WBC/ Neutropenia

Miscellaneous: Fever, Weight gain

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

Salivary hypersecretion, somnolence, weight increased, dizziness (excluding vertigo), constipation, insomnia, nausea, vomiting, dyspepsia

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 with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

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: photosensitivity, 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 vein 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

4.9 Overdose
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.

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 ODT.

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

5. PHARMACOLOGICAL PROPERTIES
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 type 2 (D2) and the serotonin type 2A (5-HT2A) receptors. Clozapine ODT also acts as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors

5.1 Pharmacodynamic Properties
Clozapine demonstrated binding affinity to the following receptors: histamine H1 (Ki 1.1 nM), adrenergic α1A (Ki 1.6 nM), serotonin 5-HT6 (Ki 4 nM**)**, serotonin 5-HT2A (Ki 5.4 nM), muscarinic M1 (Ki 6.2 nM), serotonin 5-HT7 (Ki 6.3 nM), serotonin 5-HT2C (Ki 9.4 nM), dopamine D4 (Ki 24 nM), adrenergic α2A (Ki 90 nM), serotonin 5-HT3 (Ki 95 nM), serotonin 5HT1A (Ki 120 nM), dopamine D2 (Ki 160 nM), dopamine D1 (Ki 270 nM), dopamine D5 (Ki 454 nM), and dopamine D3 (Ki 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.

5.2 Pharmacokinetic Properties

Absorption:

Following a dosage of 100 mg b.i.d., the average steady-state peak plasma concentration was 413 ng/mL (range: 132-854 ng/mL), occurring at the average of 2.3 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady-state was 168 ng/mL (range: 45-574 ng/mL), after 100 mg b.i.d. dosing.

For Clozapine ODT 200 mg tablets, food significantly increased the Cmin,ss of clozapine by 21%. However, this increase is not clinically significant. The mean AUCss and Cmax,ss of clozapine under fed conditions were equivalent to those under fasted conditions. Food delayed clozapine absorption by 1.5 hours, from a median Tmax of 2.5 hours under fasted conditions to 4 hours under fed conditions.

When Clozapine ODT was administered after a high-fat meal, the Cmax 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 Cmax is not clinically significant. Therefore, Clozapine ODT 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.

Metabolism and Excretion: Clozapine is almost completely metabolized prior to excretion, and only trace amounts of unchanged drug are detected in the urine and feces. Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2, CYP2D6, and CYP3A4. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated, and *N*-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite (norclozapine) to have only limited activity, while the hydroxylated and *N*-oxide derivatives were inactive. The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life of 12 hours (range: 4-66 hours), after achieving steady-state with 100 mg twice daily dosing.

A comparison of single-dose and multiple-dose administration of clozapine demonstrated that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration-dependent pharmacokinetics. However, at steady-state, approximately dose-proportional changes with respect to AUC (area under the curve), peak, and minimum clozapine plasma concentrations were observed after administration of 37.5, 75, and 150 mg twice daily.

Drug-Drug Interaction Studies

Fluvoxamine

A pharmacokinetic study was conducted in 16 schizophrenic patients who received clozapine under steady-state conditions. After coadministration of fluvoxamine for 14 days, mean trough concentrations of clozapine and its metabolites, *N*-desmethylclozapine and clozapine *N*-oxide, were elevated about three-fold compared to baseline steady-state concentrations.

Paroxetine, Fluoxetine, and Sertraline

In a study of schizophrenic patients (n=14) who received clozapine under steady-state conditions, coadministration of paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline.

Specific Population Studies

Renal or Hepatic Impairment

No specific pharmacokinetic studies were conducted to investigate the effects of renal or hepatic impairment on the pharmacokinetics of clozapine. Higher clozapine plasma concentrations are likely in patients with significant renal or hepatic impairment when given usual doses.

CYP2D6 Poor Metabolizers
A subset (3%–10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses.

5.3 Preclinical Safety Data
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses up to 0.3 times and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 900 mg/day on a mg/m^2 body surface area basis.

Mutagenesis
Clozapine was not genotoxic when tested in the following gene mutation and chromosomal aberration tests: the bacterial Ames test, the *in vitro* mammalian V79 in Chinese hamster cells, the *in vitro* unscheduled DNA synthesis in rat hepatocytes, or the *in vivo* micronucleus assay in mice.

Impairment of Fertility
Clozapine had no effect on any parameters of fertility, pregnancy, fetal weight, or postnatal development when administered orally to male rats 70 days before mating and to female rats for 14 days before mating at doses up to 0.4 times the MRHD of 900 mg/day on a mg/m^2 body surface area basis.

6. PHARMACEUTICAL PARTICULARS
6.1 Shelf-life: 24 Months

6.2 Special Precautions for Storage
Store Clozapine orodispersible tablets at below 25°C, Protect from light and moisture

KEEP OUT OF REACH OF CHILDREN.

Clozapine ODT must remain in the original package until used by the patient.

Drug dispensing should not ordinarily exceed a weekly supply. If a patient is eligible for WBC count and ANC testing every 2 weeks, then a 2 week supply of Clozapine Oro Dispersible Tablets can be dispensed. If a patient is eligible for WBC count and ANC testing every 4 weeks, then a 4 week supply of Clozapine Oro Dispersible Tablets can be dispensed. Dispensing should be contingent upon the WBC count and ANC testing results

6.3 Nature and Contents of Container
Clozapine ODT is available as 12.5 mg, 25 mg, 50 mg, 100 mg and 200 mg strengths and it is packaged in Alu-Alu blisters.

Manufactured by:
Alkem Laboratories Ltd
Central Pendam Block,
Dugailaka, Kumrek,
Rangpo,
East Sikkim -737 132

Marketed By:
Alkem Laboratories Ltd
Alkem House,
Senapati Bapat Marg,
Lower Parel, Mumbai 400 013