For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

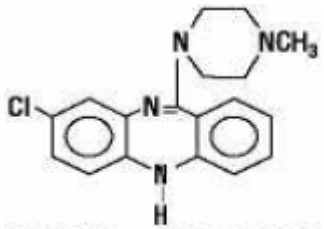
LOZAPIN
(Clozapine Tablets I.P.)

COMPOSITION
LOZAPIN-25
Each uncoated tablet contains:
Clozapine I.P.....25mg

LOZAPIN-50
Each uncoated tablet contains:
Clozapine I.P.....50 mg

LOZAPIN-100
Each uncoated tablet contains:
Clozapine I.P.....100 mg

DESCRIPTION
Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics. Clozapine is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.



$C_{18}H_{19}ClN_4$ Mol. wt. 326.83

CLINICAL PHARMACOLOGY
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-HT_2A) receptors. Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and other dopaminergic and serotonergic receptors.

Pharmacodynamics
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 5-

HT1A (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.

PHARMACOKINETICS

Absorption

In man, Clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a Clozapine solution. Following oral administration of Clozapine 100 mg twice daily, the average steady-state peak plasma concentration was 319 ng/mL (range: 102 to 771 ng/mL), occurring at the average of 2.5 hours (range: 1 to 6 hours) after dosing. The average minimum concentration at steady state was 122 ng/mL (range: 41 to 343 ng/mL), after 100 mg twice daily dosing. Food does not appear to affect the systemic bioavailability of Clozapine. Thus, Clozapine may be administered with or without food.

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 to12 hours), compared to a mean elimination half-life of 12 hours (range: 4-66 hours), after achieving steady state with 100mg 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.

INDICATIONS

Indicated in the management of Schizophrenic patients

DOSAGE AND ADMINISTRATION

Required Laboratory Testing Prior to Initiation and During Therapy

Prior to initiating treatment with Clozapine, obtain a complete blood count (CBC) with differential. The absolute neutrophil count (ANC) must be greater than or equal to 2000/mm^3 and the WBC must be greater than or equal to 3500 mm^3 in order to initiate treatment. To continue treatment, the ANC and WBC must be monitored regularly.

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.

Maintenance Treatment

Generally, it is recommended that patients responding to Clozapine continue maintenance treatment on their effective dose beyond the acute episode.

Discontinuation of Treatment

In the event of planned termination of Clozapine therapy, reduce the dose gradually over a period of 1 to 2 weeks. If abrupt discontinuation is necessary (because of agranulocytosis or another medical condition, for example), monitor carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.

Re-Initiation of Treatment

When restarting Clozapine in patients who have discontinued Clozapine (i.e., 2 days or more since the last dose), re-initiate with 12.5-mg once daily or twice daily. This is necessary to minimize the risk of hypotension, bradycardia, and syncope. 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).

Renal or Hepatic Impairment or CYP2D6 Poor Metabolizers

It may be necessary to reduce the Clozapine dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolizers

CONTRAINDICATIONS

History of Clozapine-induced Agranulocytosis or Severe Granulocytopenia

Clozapine is contraindicated in patients with a history of clozapine-induced agranulocytosis or severe granulocytopenia.

Hypersensitivity

Clozapine is contraindicated in patients with a history of hypersensitivity to clozapine (e.g., photosensitivity, vasculitis, erythema multiforme, or Stevens-Johnson Syndrome) or any other component of Clozapine.

WARNINGS AND PRECAUTIONS

General

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 the treatment of patients with dementia-related psychosis.

Agranulocytosis

Because of the significant risk of agranulocytosis, a potentially life-threatening adverse event clozapine should be reserved for use in the following indications:

1) For treatment of severely ill schizophrenic patients who fail to show an acceptable response to adequate courses of standard drug treatment for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Consequently, before initiating treatment with clozapine; it is strongly recommended that a patient be given at least 2 trials, each with a different standard drug product for schizophrenia, at an adequate dose, and for an adequateduration.

2) For reducing the risk for recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of reexperiencing suicidal behavior. Clozapine is available only through a distribution system that ensures monitoring of white blood cell (WBC) count and absolute neutrophil count (ANC) according to the schedule described below prior to delivery of the next supply of medication.

Patients who are being treated with clozapine must have a baseline WBC count and ANC before initiation of treatment, and a WBC count and ANC every week for the first 6 months. thereafter, if acceptable WBC counts and ANC (wbc $\geq$3500/mm^3 and anc $\geq$2000/mm^3) have been maintained during the first 6 months of continuous therapy, WBC counts and ANC can be monitored every 2 weeks for the next 6 months. thereafter, if acceptable wbc counts and anc (wbc $\geq$3500/mm^3 and anc $\geq$2000/mm^3) have been maintained during the second 6 months of continuous therapy, wbc count and anc can be monitored every 4 weeks. When treatment with clozapine is discontinued (regardless of the reason), wbc count and anc must be monitored weekly for at least 4 weeks from the day of discontinuation or until wbc $\geq$3500/mm^3 and anc $\geq$2000/mm^3.

WBC Count and ANC Monitoring Schedule

Table 1 provides a summary of the frequency of monitoring that should occur based on various stages of therapy (e.g., initiation of therapy) or results from WBC count and ANC monitoring tests (e.g., moderate leukopenia). The text that follows should be consulted for additional details regarding the treatment of patients under the various conditions (e.g., severe leukopenia).

Table 1. Frequency of Monitoring based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests

Situation	Hematological Values for Monitoring	Frequency of WBC Count and ANC Monitoring
Initiation of therapy	WBC count $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$ Note: Do not initiate in patients with a history of clozapine-induced agranulocytosis or severe granulocytopenia.	Weekly for 6 months
6 to 12 months of therapy	WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$	Every 2 weeks for 6 months
12 months of therapy	WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$	Every 4 weeks ad infinitum
Immature forms present	N/A	Repeat WBC and ANC
Discontinuation of therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$
Substantial drop in WBC or ANC	Single drop or cumulative drop within 3 weeks of: WBC $\geq 3000/mm^3$ or ANC $\geq 1500/mm^3$	1. Repeat WBC and ANC 2. If repeat values are: WBC $3000/mm^3$ to 3500 and ANC $> 2000/mm^3$, then monitor twice weekly
Mild leukopenia and/or Mild granulocytopenia	If WBC 3000 mm^3 to $< 3500/mm^3$ and/or ANC $1500/mm^3$ to $< 2000/mm^3$	Twice weekly until WBC $>3500/mm^3$ and ANC $>2000/mm^3$ then return to previous monitoring frequency
Moderate leukopenia and/or Moderate granulocytopenia	WBC $2000/mm^3$ to $< 3000/mm^3$ and/or ANC $1000/mm^3$ to $< 1500/mm^3$	1. Interrupt therapy 2. Daily until WBC $>3000/mm^3$ and ANC $>1500/mm^3$ 3. Twice weekly until WBC $>3500/mm^3$ and ANC $>2000/mm^3$ 4. May rechallenge when WBC $>3500/mm^3$ and ANC $>2000/mm^3$ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum

Situation	Hematological Values for Monitoring	Frequency of WBC Count and ANC Monitoring
Severe leukopenia and/or Severe granulocytopenia	WBC count < 2000/mm^3 and/or ANC < 1000/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: – Daily until WBC > 3000/mm^3 and ANC >1500/mm^3 – Twice weekly until WBC > 3500/mm^3 and ANC > 2000/mm^3 – Weekly after WBC > 3500/mm^3
Agranulocytosis	ANC < 500/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: – Daily until WBC > 3000/mm^3 and ANC > 1500/mm^3 – Twice weekly until WBC > 3500/mm^3 and ANC > 2000/mm^3 – Weekly after WBC > 3500/mm^3
WBC = White blood cell ANC = Absolute neutrophil count		

Decrements in WBC Count and/or ANC

Consult Table 1 above to determine how to monitor patients who experience decrements in WBC count and ANC at any point during treatment. Additionally, patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.

Nonrechallengeable Patients

If the total WBC count falls below 2000/mm^3 or the ANC falls below 1000/mm^3, bone marrow aspiration should be considered to ascertain granulopoietic status and patients should not be rechallenged with clozapine. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients discontinued from clozapine therapy due to significant granulopoietic suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on reexposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during clozapine therapy, a single, national master file (i.e., Nonrechallengeable Database) is maintained confidentially.

Treatment of Rechallengeable Patients

Patients may be rechallenged with clozapine if their WBC count does not fall below 2000/mm^3 and the ANC does not fall below 1000/mm^3. However, analysis of data from the Clozapine National Registry suggests that patients who have an initial episode of moderate leukopenia

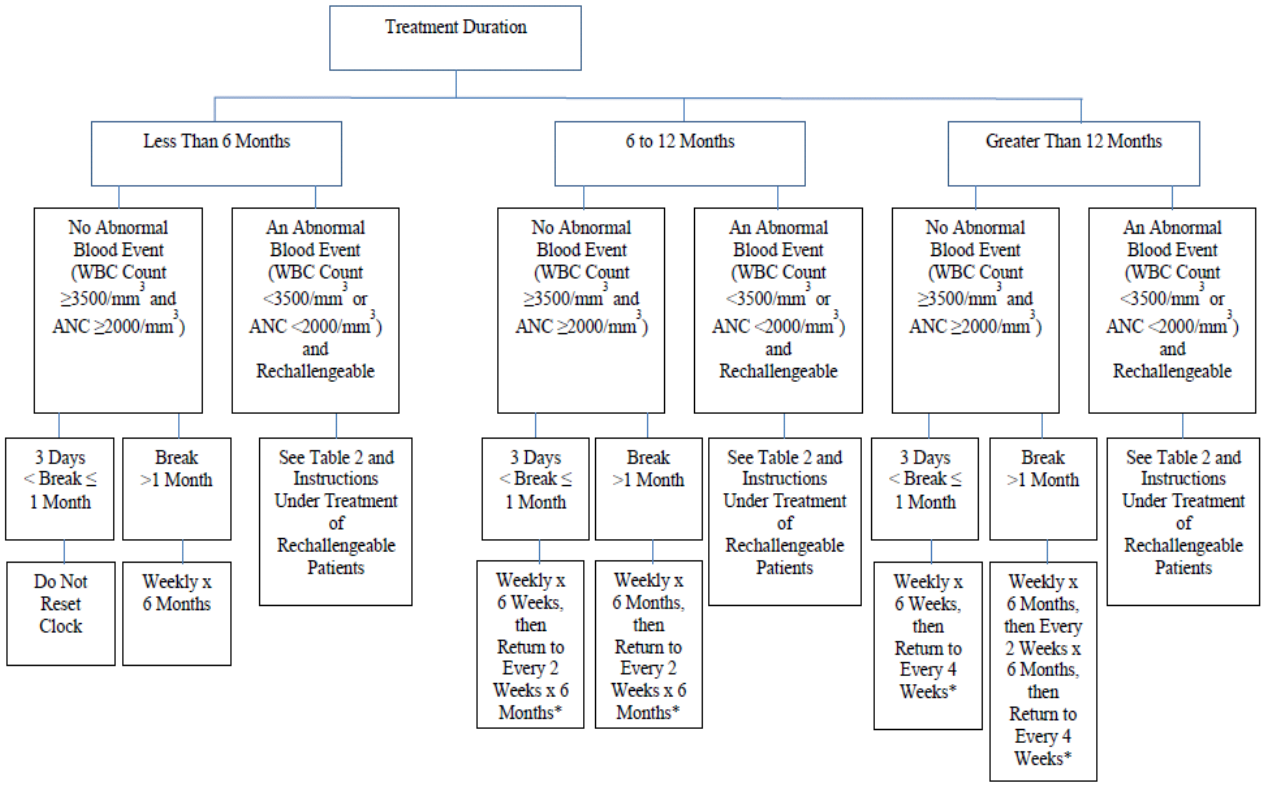
(3000/mm^3>WBCC2000/mm^3) have up to a 12-fold increased risk of having a subsequent episode of agranulocytosis when rechallenged compared to the full cohort of patients treated with clozapine. Although clozapine therapy may be resumed if no symptoms of infection develop, and when the WBC count rises above 3500/mm^3 and the ANC rises above 2000/mm^3, prescriber are strongly advised to consider whether the benefit of continuing clozapine treatment outweighs the increased risk of agranulocytosis.

Analyses of the Clozapine National Registry have shown an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, as noted in Table 1 above, patients must undergo weekly WBC count and ANC monitoring for one year following recovery from an episode of moderate leukopenia and/or moderate granulocytopenia regardless of when the episode develops. If acceptable WBC counts and ANC (WBC ≥3500/mm^3 and ANC ≥2000/mm^3) have been maintained during the year of weekly monitoring, WBC counts can be monitored every 2 weeks for the next 6 months. If acceptable WBC counts and ANC (WBC ≥3500/mm^3 and ANC ≥2000/mm^3) continue to be maintained during the 6 months of every 2 week monitoring, WBC counts can be monitored every 4 weeks thereafter, ad infinitum.

Interruptions in Therapy

Figure 1. Provides instructions regarding reinitiating therapy and subsequently the frequency of WBC count and ANC monitoring after a period of interruption.

Figure 1. Resuming Monitoring Frequency after Interruption of Therapy



*Transitions to reduce frequency of monitoring only permitted if all WBC counts ≥3500/mm^3 and ANCs ≥2000/mm^3.

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. Consider reducing the dose if hypotension occurs. When restarting patients who have had even a brief interval off Clozapine (i.e., 2 days or more since the last dose), re-initiate treatment at 12.5 mg once daily or twice daily.

Use Clozapine 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 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 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 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. However, if the benefit of Clozapine treatment is judged to outweigh the potential risks of recurrent myocarditis or cardiomyopathy, the clinician may consider rechallenge with Clozapine 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 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. 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 is not approved for the treatment of patients with dementia-related psychosis.

Eosinophilia

Eosinophilia, defined as a blood eosinophil count of greater than 700/mm^3, 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 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 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.

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 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 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, 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, and electrolyte abnormalities.

Prior to initiating treatment with Clozapine, 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 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.

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, 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 is primarily metabolized by CYP isoenzymes 1A2, 2D6, and 3A4. Concomitant treatment with inhibitors of these enzymes can increase the concentration of Clozapine.

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.

Metabolic Changes

Atypical antipsychotic drugs, including Clozapine 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. 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 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. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using Clozapine, is recommended.

Weight Gain
Weight gain has occurred with the use of antipsychotics, including Clozapine. Monitor weight during treatment with Clozapine. Table 6 summarizes the data on weight gain by the duration of exposure pooled from 11 studies with Clozapine and active comparators. The median duration of exposure was 609, 728, and 42 days, in the Clozapine, olanzapine, and chlorpromazine group, respectively.

Neuroleptic Malignant Syndrome
Antipsychotic drugs including Clozapine 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., agranulocytosis, 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 comorbid 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 agranulocytosis 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 has potent anticholinergic effects. Treatment with Clozapine can result in CNS and peripheral anticholinergic toxicity. Use with caution in the presence of narrow-angle glaucoma, concomitant anticholinergic medications, prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to significant adverse reactions.

Treatment with Clozapine 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 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 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. 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 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 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 or other antipsychotics or other patient populations. Clozapine 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
If abrupt discontinuation of Clozapine is necessary (because of agranulocytosis 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.

DRUG INTERACTIONS

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 concomitantly with drugs that are inducers or inhibitors of these enzymes.

CYP1A2 Inhibitors
Concomitant use of Clozapine and CYP1A2 inhibitors can increase plasma levels of clozapine, potentially resulting in adverse reactions. Reduce the Clozapine dose to one third of the original dose when Clozapine is coadministered with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin, or enoxacin). The Clozapine 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 is coadministered with these inhibitors. Consider reducing the Clozapine dosage if necessary.

CYP2D6 and CYP3A4 Inhibitors
Concomitant treatment with Clozapine 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 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. 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 dose if used concomitantly with inducers of these enzymes. However, concomitant use of Clozapine and strong CYP3A4 inducers is not recommended.

Consider reducing the Clozapine 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. 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 to Affect Other Drugs
Concomitant use of Clozapine with other drugs metabolized by CYP2D6 can increase levels of these CYPD26 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).

USE IN SPECIFIC POPULATIONS
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 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.

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/m^2 body surface area basis.

In peri/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 F1or F2 generations at doses up to 0.4 times the MRHD of 900 mg/day on an mg/m^2 body surface area basis.

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.

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 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. 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 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.

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.

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.

ADVERSE REACTIONS

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

- Agranulocytosis
- 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

Clinical Trials Experience
The most commonly reported adverse reactions ($\geq$5%) across Clozapine clinical trials were: CNS reactions, including sedation, dizziness/vertigo, headache, and tremor; cardiovascular reactions, including tachycardia, hypotension, and syncope; autonomic nervous system reactions, including hypersalivation, sweating, dry mouth, and visual disturbances; gastrointestinal reactions, including constipation and nausea; and fever. Table 8 summarizes the most commonly reported adverse reactions ($\geq$5%) in Clozapine-treated patients (compared to chlorpromazine-treated patients) in the pivotal, 6-week, controlled trial in treatment-resistant schizophrenia.

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
Hypotension	13	38
Fever (hyperthermia)	13	4
Hypersalivation	13	1
Hypertension	12	5
Headache	10	10
Nausea/vomiting	10	12
Dry mouth	5	20

Table 9 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.

Adverse Reactions (≥ 2%) Reported in Clozapine-treated Patients (N=842) across all Clozapine Studies (excluding the 2-year InterSePT™ Study)

Body System Adverse Reaction*	CLOZAPINE N = 842 Percentage of Patients
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†
Hypotension	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

Body System **Adverse Reaction***	**CLOZAPINE** **N = 842** **Percentage of Patients**
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 CLOZARIL.

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.

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 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.

Gastrointestinal System

Acute pancreatitis, dysphagia, salivary gland swelling, colitis.

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
Hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, skin pigmentation disorder and Stevens - Johnson syndrome.

Musculoskeletal System
Myasthenic syndrome, rhabdomyolysis and systemic lupus erythematosus.

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

Hemic and Lymphatic System
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.

OVERDOSE

Human Experience

The most commonly reported signs and symptoms associated with clozapine overdose are: altered states of consciousness, including drowsiness, delirium and coma; tachycardia; hypotension; respiratory depression or failure; hypersalivation. Aspiration pneumonia and cardiac arrhythmias have also been reported. Seizures have occurred in a minority of reported cases. 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.

Management of Overdose

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdosage. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Additional surveillance should be continued for several days because of the risk of delayed effects. Avoid epinephrine and derivatives when treating hypotension, and quinidine and procainamide when treating cardiac arrhythmia.

Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.

There are no specific antidotes for Clozapine. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

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

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

Expiry date:
Do not use later than the date of expiry.

Storage:
Sore at a temperature not exceeding 30°c, protected from light and moisture.
Keep out of reach of children.

Presentation:
LOZAPIN-25, LOZAPIN-50, LOZAPIN-100 is available in Blister of 10 Tablets

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

LOZA/OCT 2014/Ver 02