CLOZAPINE
NIRVA®
25 mg and 100 mg Tablet
ANTIPSYCHOTIC

FORMULATION
Each tablet contains: Clozapine……………………………………………25 or 100 mg

PRODUCT DESCRIPTIONS
Clozapine (Nirva) 25 mg tablet is a light yellow, plain 9/32" diameter round tablet, bisected on one side. Clozapine (Nirva) 100 mg tablet is a light yellow, plain 7/16" diameter round tablet, bisected on one side.

PHARMACOLOGY
Clozapine is a dibenzodiazepine-derivative atypical antipsychotic agent. While clozapine shares some of the pharmacologic actions of other antipsychotic agents, it is classified as an "atypical" antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine-mediated behaviors differ from those exhibited by more typical antipsychotic drugs. In pharmacological experiments, clozapine does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behavior. Clozapine has only weak dopamine-receptor-blocking activity at D_1, D_2, D_3, and D_5 receptors, but shows high potency for the D_4 receptor. This evidence, consistent with the view that clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of clozapine from extrapyramidal side effects. In addition, clozapine has potent anti-α-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties. Clinically, clozapine produced rapid and marked sedation with strong antipsychotic effects in patients resistant to other drug treatment. In these patients, clozapine has been shown to be effective in the relief of both positive and negative symptoms of schizophrenia. In contrast to typical antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynecomastia, amenorrhea, galactorrhea, and impotence.

PHARMACOKINETICS
Clozapine is well absorbed from the gastrointestinal tract (90 to 95%); neither the rate nor extent of absorption is affected by food intake. However, clozapine is subject to moderate first-pass metabolism resulting in an absolute bioavailability of 50 to 60%. After administration of 100 mg tablet twice a day, 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). Clozapine is rapidly and extensively distributed throughout the body and crosses the blood brain barrier freely. Its volume of distribution is 1.6 L/kg. Clozapine is approximately 97% bound to plasma proteins. Clozapine is metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. It may undergo N-demethylation, N-oxidation, 3'-carbon oxidation, epoxidation of the chlorine-containing aromatic ring, substitution of chlorine by hydroxyl or thiomethyl groups, and sulfur oxidation. A glucuronide metabolite, tentatively identified as a quaternary ammonium N-glucuronide of clozapine, has also been identified. Metabolism of clozapine may occur by one or more of these routes. The desmethyl metabolite of clozapine (norclozapine) has limited activity while the hydroxylated and N-oxide derivatives are inactive. Approximately 50% of the administered dose is excreted as metabolites in the urine and 30% in the feces. The mean elimination half-life ($t_{1/2}$) of clozapine after a single 75-mg dose was eight hours (range: 4 to12 hours) compared to 12 hours (range: 4 to 66 hours) at steady state with 100 mg twice a day dosing. The elimination $t_{1/2}$ of clozapine increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration-dependent pharmacokinetics. However, at steady state, linearly dose-proportional changes with respect to area-under-the curve (AUC), peak and minimum clozapine plasma concentration were observed after administration of clozapine 37.5 mg, 75 mg and 150 mg twice a day.

INDICATIONS
- **Treatment-Resistant Schizophrenia**
  For the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia.
- **Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders**
  For reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are considered to be at chronic risk for reexperiencing suicidal behavior, based on history and recent clinical state.
- **Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed**

DOSAGE AND ADMINISTRATION
Before initiating therapy:
- Patients should have a baseline white blood cell count (WBC) and absolute neutrophil count (ANC), a medical history and physical examination.
- Patients with a history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that include an electrocardiogram (ECG), and the patient treated only if expected benefits clearly outweigh the risks.

General Dosing Recommendations:
Clozapine may be taken with or without food.
Dosage of clozapine should be carefully adjusted according to individual requirements and response using the lowest effective dosage.
Cautious dosage titration and administration of clozapine in divided doses are necessary to minimize the risk of hypotension, seizures, and sedation.
Initiation of clozapine treatment must be restricted to those patients with a WBC count $\geq$ 3500/mm^3 (3.5×10^9/L) and an ANC $\geq$ 2000/mm^3 (2.0×10^9/L), and within standardized normal limits.
Dose adjustment is indicated in patients who are also receiving drugs that have pharmacodynamic and pharmacokinetic interactions with clozapine (e.g., benzodiazepines or selective serotonin reuptake inhibitors).

TREATMENT-RESISTANT SCHIZOPHRENIA
Starting Dose
12.5 mg (half of a 25 mg tablet) once or twice a day on the first day and then continued with daily dosage increments of **25 to 50 mg per day,** if well tolerated, to achieve a target dose of 300 to 450 mg per day by the end of two weeks.
Subsequent dosage increments should be made no more than once or twice a week, in increments not to exceed 100 mg.
Therapeutic Dose Range: 300 to 450 mg per day given in divided doses;
The total daily dose may be divided unevenly, with the larger portion at bedtime.
Maximum Dose: 900 mg per day
To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (i.e., not exceeding 100 mg) are permissible up to 900 mg per day. The possibility of increased adverse reactions, particularly seizures, occurring at doses over 450 mg per day must be considered.
Maintenance Dose
After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least six months. If the daily dose does not exceed 200 mg, once a day administration in the evening may be appropriate. Patients should be periodically reassessed to determine the need for maintenance treatment because of the significant risk associated with clozapine.
Discontinuation of Therapy
Discontinuation of clozapine therapy should be done with a gradual dose reduction over a 1- to 2- week period.
If abrupt discontinuation is required (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound (e.g., profuse sweating, headache, nausea, vomiting, and diarrhea).
Reinitiation of Treatment in Patients Previously Discontinued
When reinitiating treatment in patients who have had even a brief interval off clozapine, i.e., two days or more since the last dose, it is recommended that treatment be reinitiated with 12.5 mg (half of a 25 mg tablet) once or twice a day. If this dose is well tolerated, titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be retitrated with extreme caution even after 24 hours of discontinuation. The reexposure of a patient might enhance the risk of occurrence of an untoward event and increase its severity. Such phenomena occur when immune-mediated mechanisms are responsible. Therefore, during the reinitiation of treatment, additional caution is advised.
Patients discontinued for WBC counts below 2,000/mm^3 or an ANC below 1,000/mm^3 must not be restarted on clozapine.
Switching From a Previous Antipsychotic Therapy to Clozapine
Clozapine should not be used in combination with other antipsychotics. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that typical antipsychotic should first be discontinued by tapering the dosage downwards.Based on the clinical circumstances, the physician should judge whether or not to discontinue the other antipsychotic therapy before initiating treatment with clozapine.

REDUCING THE RISK OF RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER
The dosage and administration recommended to patients with treatment-resistant schizophrenia should be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behavior.
In order to maintain the reduction of risk for suicidal behavior, a course of treatment with clozapine of at least two years is recommended. After two years, the patient's risk of suicidal behavior should be assessed. If the physician's assessment indicates that a significant risk for suicidal behavior is still present, treatment with clozapine should be continued. Then, the decision to continue treatment with clozapine should be revisited at regular intervals, based on thorough assessments of the patient's risk for suicidal behavior during treatment. If the physician determines that the patient is no longer at risk for suicidal behavior, treatment with clozapine may be discontinued and treatment of the underlying disorder with an antipsychotic drug to which the patient has previously responded may be resumed.

PSYCHOTIC DISORDERS OCCURRING DURING THE COURSE OF PARKINSON'S DISEASE, IN CASES WHERE STANDARD TREATMENT HAS FAILED
Starting Dose: 12.5 mg (half of a 25 mg tablet), taken in the evening.
Subsequent dose increases must be made by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.
Mean Effective Dose: 25 to 37.5 mg per day
Dosage may be cautiously increased by increments of 12.5 mg per week, in cases when the treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response.
The dose of 50 mg per day should only be exceeded in exceptional cases, and the **maximum dose of 100 mg per day** must never be exceeded.
Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.
In cases of complete remission of psychotic symptoms for at least two weeks, an increase in anti-parkinsonian drug is possible if indicated on the basis of motor status. If this results in the recurrence of psychotic symptoms, clozapine dosage may be increased by increments of 12.5 mg per week up to a maximum of 100 mg per day, taken in one or two divided doses.
Ending therapy: A gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.
Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis. In this case, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

SPECIAL POPULATION:
In patients with a history of seizures or suffering from renal or cardiovascular disorders:
Initial dose: 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.
Geriatric:
Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg per day.
Or, as prescribed by a physician.

CONTRAINDICATIONS
- Known hypersensitivity to clozapine or any ingredient of the product
- In patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of clozapine-induced agranulocytosis or severe granulocytopenia
- In patients who are unable to undergo regular blood tests
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy)
- Impaired bone marrow function
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions
- Circulatory collapse and/or CNS depression of any cause
- Severe renal or cardiac disorders (e.g., myocarditis)
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure
- Concomitant use with long-acting depot antipsychotics (which have myelosuppressive potential) since these cannot be rapidly removed from the body in situations where this may be required (e.g., Neutropenia). (See Drug Interactions).

WARNINGS AND PRECAUTIONS
Agranulocytosis
Because of a significant risk of agranulocytosis, a potentially life-threatening adverse event, clozapine should be reserved for use in 1) the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment, or 2) for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of re-experiencing suicidal behavior. Patients being treated with clozapine must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment as well as regular WBC counts and ANCs during treatment and for at least four weeks after discontinuation of treatment.
Seizures
Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Caution should be used when administering clozapine to patients having a history of seizures or other predisposing factors. Patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others.
Myocarditis
Analyses of postmarketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued.
Other Adverse Cardiovascular and Respiratory Effects
Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine, i.e., two or more days since the last dose, treatment should be started with 12.5 mg once or twice a day. Since collapse, respiratory arrest and cardiac arrest during initial treatment has occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.
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 seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the 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. 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.

Agranulocytosis, defined as an ANC less than 500/mm^3, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%. All these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. Agranulocytosis can be fatal if not detected early and therapy interrupted.
It is advised to avoid clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.
Risk factors
Patients who have developed agranulocytosis during clozapine therapy are at increased risk of subsequent episodes of agranulocytosis. Except for bone marrow suppression during initial clozapine therapy, there are no other established risk factors for the development of agranulocytosis in association with clozapine use. Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have a serious underlying medical illness; such patients may also be at particular risk with clozapine, although this has not been definitely shown.
WBC Count and ANC Monitoring Schedule
WBC counts and differential blood counts must be done within 10 days prior to initiating clozapine treatment to ensure that only patients with normal WBC counts and ANC will receive clozapine. The current recommendations for WBC count and ANC monitoring based on the stage of therapy and the results from WBC and ANC monitoring are provided in Table 1.

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

Hematological Values	Frequency of WBC and ANC Monitoring
Initiation of Therapy	
WBC $\geq$ 3,500/mm^3 ANC $\geq$ 2,000/mm^3 Note: Do not initiate in patients with: 1) History of myeloproliferative disorder or 2) Clozapine-induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 - 12 months of therapy	
All results for WBC $\geq$ 3,500/mm^3 and ANC $\geq$ 2,000/mm^3	Every 2 weeks for 6 months
12 months of therapy	
All results for WBC $\geq$ 3,500/mm^3 and ANC $\geq$ 2,000/mm^3	Every 4 weeks thereafter
Immature forms present	
Not applicable	Repeat WBC and ANC
Discontinuation of Therapy	
Not applicable	Weekly for at least 4 weeks from day of discontinuation or until WBC $\geq$ 3,500/mm^3 and ANC $\geq$ 2,000/mm^3
Substantial decrease in WBC or ANC	
Single decrease or cumulative decrease within 3 weeks of WBC $\geq$ 3,000/mm^3 or ANC $\geq$ 1,500/mm^3	1. Repeat WBC and ANC. Carefully monitor for manifestations of infection.** 2. If repeat values are 3,000/mm^3 $\leq$ WBC $\leq$ 3,500/mm^3 and ANC < 2,000/mm^3, then monitor twice a week.
Mild Leukopenia / Mild Granulocytopenia	
3,500/mm^3 > WBC $\geq$ 3,000/mm^3 and/or 2,000/mm^3 > ANC $\geq$ 1,500/mm^3	Monitor twice a week until WBC > 3,500/mm^3 and ANC > 2,000/mm^3, then resume previous monitoring frequency. Carefully monitor for manifestations of infection.**
Moderate Leukopenia / Moderate Granulocytopenia	
3,000/mm^3 > WBC $\geq$ 2,000/mm^3 and/or 1,500/mm^3 > ANC $\geq$ 1,000/mm^3	1. Interrupt therapy and carefully monitor for manifestations of infection.** 2. Monitor daily until WBC > 3,000/mm^3 and ANC > 1,500/mm^3 3. Monitor twice a week until WBC > 3,500/mm^3 and ANC > 2,000/mm^3 4. May rechallenge when WBC > 3,500/mm^3 and ANC > 2,000/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 indefinitely.
Severe Leukopenia / Severe Granulocytopenia	
WBC < 2,000/mm^3 and/or ANC < 1,000/mm^3	1. Discontinue therapy and do not rechallenge patient.* Carefully monitor for manifestations of infection.** 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: • Daily until WBC > 3,000/mm^3 and ANC >1,500/mm^3 • Twice a week until WBC > 3,500/mm^3 and ANC > 2,000/mm^3 • Weekly after WBC > 3,500/mm^3
Agranulocytosis	
ANC $\leq$ 500/mm^3	1. Discontinue therapy and do not rechallenge patient.* Carefully monitor for manifestations of infection.** 2. Monitor until normal and for at least four weeks from day of discontinuation as follows: • Daily until WBC > 3,000/mm^3 and ANC >1,500/mm^3 • Twice a week until WBC > 3,500/mm^3 and ANC > 2,000/mm^3 • Weekly after WBC > 3,500/mm^3

* Agranulocytosis develops upon rechallenge, often with a shorter latency.
** Carefully monitor for flu-like symptoms or other manifestation of infection; institute appropriate anti-infective therapy if necessary.

Nonrechallengeable Patients
Bone marrow aspiration should be considered to determine granulopoietic status and patients should not be rechallenged with clozapine if the total WBC count falls below 2,000/mm^3 or the ANC falls below 1,000/mm^3. 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 done and an appropriate antibiotic regimen instituted.
Treatment of Rechallengeable Patients
Patients may be rechallenged with clozapine if their WBC count does not fall below 2,000/mm^3 and the ANC does not fall below 1,000/mm^3. Patients who have an initial episode of moderate leukopenia (3,000/mm^3 > WBC $\geq$ 2,000/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 3,500/mm^3 and the ANC rises above 2,000/mm^3, prescribers are strongly advised to consider whether the benefit of continuing clozapine treatment outweighs the increased risk of agranulocytosis.
There is an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, 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 $\geq$ 3,500/mm^3 and ANC $\geq$ 2,000/mm^3) have been maintained during the year of weekly monitoring, WBC counts can be monitored every two weeks for the next six months. If acceptable WBC counts and ANC (WBC $\geq$ 3,500/mm^3 and ANC $\geq$ 2,000/mm^3) continue to be maintained during the six months of every two week monitoring, WBC counts can be monitored every four weeks thereafter.
Interruptions of Therapy
If clozapine therapy is reinitiated after interruption of therapy, WBC counts and ANC should be monitored after reinitiating therapy based on the duration of previous therapy, length of interruption of therapy, and previous WBC counts and ANC in the patient according to the schedule in Table 2.

Table 2. WBC and ANC Monitoring for Clozapine Reinitiation

Previous therapy duration < 6 months, with no abnormal blood event (WBC $\geq$ 3,500/mm^3 and ANC $\geq$ 2,000/mm^3) and interruption in therapy $\geq$ 3 days but $\leq$ 1 month	Continue with weekly WBC and ANC monitoring where left off in schedule; do not restart 6-month period. When 6-month period complete, may decrease monitoring frequency to every other week.
Previous therapy duration < 6 months, with no abnormal blood event and interruption in therapy > 1 month	Monitor WBC and ANC weekly for additional 6 months before decreasing to biweekly testing.
Previous therapy duration < 6 months, with abnormal blood event (WBC < 3,500/mm^3 or ANC < 2,000/mm^3) but rechallengeable *	See Table 1
Previous therapy duration 6 to12 months, with no abnormal blood event and interruption in therapy $\geq$ 3 days but $\leq$ 1 month	Monitor WBC and ANC weekly for 6 weeks, then resume monitoring every other week for an additional 6 months
Previous therapy duration 6 to12 months, with no abnormal blood event and interruption in therapy > 1 month	Monitor WBC and ANC weekly for 6 months, then resume monitoring every other week for an additional 6 months.
Previous therapy duration 6 to12 months, with abnormal blood event (WBC < 3,500/mm^3 or ANC < 2,000/mm^3) but rechallengeable *	See Table 1
Previous therapy duration > 12 months, with no abnormal blood event and interruption in therapy $\geq$ 3 days but $\leq$ 1 month	Monitor WBC and ANC weekly for 6 weeks, then resume monitoring every 4 weeks.
Previous therapy duration > 12 months, with no abnormal blood event and interruption in therapy > 1 month	Monitor WBC and ANC weekly for 6 months, then resume monitoring every other week for an additional 6 months, then resume monitoring every 4 weeks.**
Previous therapy duration > 12 months, with abnormal blood event (WBC < 3,500/mm^3 or ANC < 2,000/mm^3) but rechallengeable *	See Table 1

* Rechallengeable defined as WBC $\geq$ 2,000/mm^3 and ANC $\geq$ 1,000/mm^3 during previous therapy
** Transition to reduce frequency of monitoring only permitted if all WBC counts are equal to or exceeding 3,500/mm^3 and ANC values are equal to or exceeding 2,000/mm^3.

Eosinophilia and Thrombocytopenia
Eosinophilia has been reported in 1% of patients who received clozapine. If a differential count reveals a total eosinophil count above 4,000/mm^3, clozapine therapy should be interrupted until the eosinophil count falls below 3,000/mm^3. In the event of thrombocytopenia, discontinuation of clozapine therapy is recommended if the platelet count falls below 50,000/mm^3.
Myocarditis, pericarditis/pericardial effusion and cardiomyopathy (see Boxed Warning)
Pericarditis/pericardial effusion and cardiomyopathy have also been reported in association with clozapine use; these reports also include fatalities. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, particularly in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g., unexplained fatigue, dyspnea, tachypnea), or symptoms that mimic myocardial infarction. Other symptoms which may be present include flu-like symptoms. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly discontinued and the patient immediately referred to a cardiologist. Patients with clozapine-related myocarditis should not be rechallenged with clozapine.
Seizures (see Boxed Warning)
Other Adverse Cardiovascular and Respiratory Effects (see Boxed Warning)
Tachycardia, which may persist throughout therapy in some cases, has been reported in 25% of patients receiving clozapine, with patients having an average increase in pulse rate of 10 to15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.Some clozapine-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including ST segment depression and flattening or inversion of T waves, which all normalize after discontinuation of clozapine. However, in clinical trials, several patients experienced significant cardiac events including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition, there have been postmarketing reports of congestive heart failure, pericarditis, and pericardial effusions. Clozapine should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.
Hyperglycemia and Diabetes Mellitus
There have been reports of severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, in patients receiving certain atypical antipsychotic agents including clozapine. Patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing.
Neuroleptic Malignant Syndrome (NMS)
There have been reports of NMS, a potentially fatal symptom complex, in association with antipsychotic drugs. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).
If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. Careful monitoring of patients is necessary since recurrences of NMS have been reported.
Tardive Dyskinesia
Patients treated with antipsychotic drugs may develop tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements. The prevalence of the syndrome appears to be highest among the elderly, particularly elderly women. There have been a few cases of tardive dyskinesia in patients on clozapine therapy who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. Nevertheless, it cannot be concluded, that clozapine is incapable of inducing this syndrome.
Fever
Patients may experience transient temperature elevations above 38°C (100.4°F), with peak incidence within the first three weeks of treatment with clozapine. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment; there may be an associated increase or decrease in WBC count.
Pulmonary Embolism
There have been reports of fatal pulmonary embolism in association with clozapine therapy. The possibility of pulmonary embolism should be considered in patients presenting with deep-vein thrombosis, acute dyspnea, chest pain, or other respiratory signs and symptoms.
Hepatic disease
Liver function tests should be done in patients in whom symptoms of possible liver dysfunction (e.g., nausea, vomiting, and/or anorexia) develop during clozapine therapy. Treatment with clozapine must be discontinued if the elevation of the values is clinically relevant [more than three times the upper limit of normal (ULN)] or if the symptoms of jaundice occur. It may be resumed only when the results of liver function tests are normal. Liver function should be closely monitored after re-introduction of the drug.
Anticholinergic Effects
Careful supervision should be done in patients with prostatic enlargement and narrow-angle glaucoma since clozapine exerts anticholinergic activity which may produce undesirable effects throughout the body. Clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus. On rare occasions, these cases have been 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.
Cerebrovascular adverse events
An increased risk of cerebrovascular adverse events has been reported in patients with dementia treated with some atypical antipsychotics. Clozapine should be used with caution in patients with dementia or risk factors for stroke.
Use in patients with concomitant illness
Caution is advised in using clozapine in patients with renal or cardiac disease.
Use in patients undergoing general anesthesia
Clozapine should be used with caution in patients undergoing general anesthesia because of the CNS effects of the drug. The anesthesiologist should be consulted regarding continuation of clozapine therapy in a patient scheduled for surgery.
Interference with cognitive and motor performance
Clozapine may impair mental and/or physical abilities, particularly during the first few days of therapy, because of initial sedation. Gradual dose escalation is recommended and should be carefully followed. Patients should be cautioned about activities requiring alertness such as driving or operating machinery.

INTERACTION WITH OTHER MEDICAMENTS
- **Bone marrow suppressants (e.g., carbamazepine, chloramphenicol), sulfonamides (e.g., co-trimoxazole), pyrazolone analgesics (e.g.,phenylbutazone), azapropazone, penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics (e.g., flupentixol, fluphenazine, haloperidol, pipotiazine, risperidone, zuclopenthixol):** Increased risk of agranulocytosis; concomitant use is not recommended
- **Ritonavir:** Plasma concentration of clozapine is increased by ritonavir (increased risk of toxicity). Concomitant use is not recommended.
- **Benzodiazepines:** Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.
- **Alcohol, antihistamines, monoamine oxidase inhibitors (MAOIs), CNS depressants, including narcotics:** Enhanced central effects; additive CNS depression and cognitive and motor performance interference when used in combination with these drugs
- **Anticholinergics (e.g., atropine-like drugs):** Clozapine potentiates the action of these drugs through additive anticholinergic activity.
- **Antihypertensives:** Clozapine can potentiate the hypotensive effects of these drugs due to its sympathomimetic antagonistic effects.
- **Type 1C antiarrhythmics (e.g., flecainide, propafenone, encainide, quinidine):** Increased risk of arrhythmias
- **Highly protein bound drugs (e.g., warfarin, digoxin):** Clozapine may increase the plasma concentrations of these drugs due to displacement from plasma proteins.
- **Tricyclic antidepressants and antimuscarinics:** Increased antimuscarinic side effects
- **Caffeine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, ciprofloxacin and amprenavir:** Increased clozapine plasma concentration
- **Omeprazole, rifampicin:** Reduced clozapine plasma concentration
- **Lithium:** Increased risk of extrapyramidal side-effects and possibly neurotoxicity
- **Phenytoin:** Metabolism of clozapine is accelerated by phenytoin (reduced clozapine plasma concentration).
- **Cimetidine:** Effects of clozapine possibly enhanced by cimetidine.
- **Citalopram:** Plasma concentration of clozapine possibly increased by citalopram (increased risk of toxicity).
- **Erythromycin:** Plasma concentration of clozapine possibly increased by erythromycin (possible increased risk of convulsions).
  Other interaction:
- **Smoking:** May decrease clozapine plasma levels, resulting in decreased effectiveness of previously effective clozapine dose.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
- **PREGNANCY AND LACTATION**
  Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women.
  Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms after delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.
  Clozapine should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
  Lactation
  Animal studies showed that clozapine is excreted in breast milk and has an effect on the breastfeeding infant; therefore, mothers under clozapine therapy should not breastfeed.
- **PEDIATRIC**
  The safety and effectiveness in pediatric patients have not been established.
- **GERIATRIC**
  Clozapine can cause orthostatic hypotension and tachycardia, which may be sustained. Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.
  Elderly patients may also be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.
  Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
Body as a Whole: Fever, chills/chills with fever, hypothermia, fatigue, weakness, pallor, malaise, sepsis
Central and Autonomic Nervous System: Drowsiness/sedation, seizures, dizziness/vertigo, dizziness (excluding vertigo), dystonia, epileptiform movements/myoclonic jerks, poor coordination, involuntary movement, histrionic movements, shakiness, Parkinsonism, tremor, disturbed sleep/nightmares, insomnia, somnolence, restlessness, hyperkinesia, hypokinesia/akinesia, agitation, rigidity, akathisia, confusion, lethargy, ataxia, slurred speech, loss of speech, stuttering, depression, anxiety, amentia, tics, delusions/hallucinations, dysarthria, amnesia/memory loss, paranoia, irritability, numbness, polydipsia, headache, delirium, abnormal electroencephalogram, exacerbation of psychosis, myoclonus, paresthesia, possible mild cataplexy, status epilepticus, obsessive compulsive symptoms
Cardiovascular: Tachycardia, bradycardia, hypotension, hypertension, electrocardiogram change/cardiac abnormality, syncope, chest pain/angina, edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, atrial or ventricular fibrillation,
Gastrointestinal: Nausea, vomiting, salivary gland swelling, salivation, salivary hypersecretion, dry mouth, dry throat, throat discomfort, constipation, abdominal discomfort/heartburn, abdominal distention, dyspepsia, diarrhea, gastroenteritis, gastric ulcer, nervous stomach, acute pancreatitis, rectal bleeding, abnormal stools, fecal impaction, hematemesis, eructation, dysphagia, intestinal obstruction/paralytic ileus
Endocrine and Metabolic: Anorexia, weight gain, weight loss, appetite increase, new onset diabetes, libido increase or decrease, impotence, priapism, abnormal ejaculation, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, hyperuricemia, hyponatremia, creatine phosphokinase elevation
Hepatic: Liver test abnormality, cholestasis, hepatitis, jaundice
Respiratory: Dyspnea, nasal congestion, coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, sneezing, aspiration, pleural effusion, pulmonary embolism, lower respiratory tract infection
Genitourinary/Reproductive: Urinary abnormalities, incontinence, urinary urgency/frequency, urinary retention, acute interstitial nephritis, dysmenorrhea, breast pain/discomfort, vaginal itch/infection
Hemic and Lymphatic System: Leukopenia/decreased WBC/neutropenia, granulocytopenia, thrombocytopenia, eosinophilia, thrombocytosis, agranulocytosis, leukocytosis, anemia, deep vein thrombosis, elevated hemoglobin/hematocrit, erythrocyte sedimentation rate increased
Dermatologic and Sensitivity Reactions: Sweating, rash, hot flashes, pruritus, eczema, bruise, dermatitis, petechiae, urticaria, erythema, hypersensitivity reactions: erythema multiforme, photosensitivity, vasculitis, Stevens-Johnson Syndrome
Musculoskeletal: Muscle weakness, pain (back, neck, legs), muscle spasm, muscle pain, twitching and joint pain, myasthenic syndrome, rhabdomyolysis
Special Senses: Visual disturbance, narrow angle glaucoma, mydriasis, eyelid disorder, bloodshot eyes, nystagmus, periorbital edema, tongue numb/sore, bitter taste, ear disorder, nosebleed

OVERDOSAGE & MANAGEMENT
In cases of acute intentional or accidental clozapine overdosage, mortality is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2,000 mg (2 g). There have been reports of patients recovering from an overdose in excess of 10,000 mg (10 g). However, in a few adults, particularly those not previously exposed to clozapine, the ingestion of doses as low as 400 mg resulted in life-threatening comatose conditions and, in one case, in death. In young children, oral ingestion of 50 to 200 mg resulted in strong sedation or coma without being lethal. The most commonly reported signs and symptoms of clozapine overdosage include altered states of consciousness and CNS depression (e.g., drowsiness, delirium, coma), tachycardia, cardiac arrhythmias, hypotension, respiratory depression or failure, aspiration, pneumonia, and hypersalivation. Seizures have occurred with overdosage in some patients. Management of clozapine overdosage includes establishing and maintaining an airway, ensuring adequate oxygenation and ventilation. Gastric lavage and/or administration of activated charcoal within the first six hours after ingestion should be considered. Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration and monitoring of electrolytes and acid-base balance are recommended. There are no specific antidotes for clozapine. Epinephrine and its derivatives should be avoided when treating hypotension because of the possibility of a "reverse epinephrine effect". Clozapine can reverse epinephrine's vasopressor effects and cause further lowering of blood pressure. Because of potential additive anticholinergic effects, quinidine or procainamide should be avoided when treating clozapine-induced arrhythmias. Forced diuresis, peritoneal dialysis, hemodialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. Close medical supervision should be continued for at least five days due to the risk of delayed effects. In managing clozapine overdosage, the physician should consider the possibility of multiple drug involvement.

STORAGE CONDITION
Keep the product out of reach and sight of children.
Store at temperatures not exceeding 30°C.

AVAILABILITY
Nirva 25 mg tablet, Alu-Blister Pack of 10's (Box of 30's)
Nirva 100 mg tablet, Alu-Blister Pack of 10's (Box of 30's)

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

*Reg. IPOPHIL
P30000012114
Date of Revision: August 2013

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