ZAPINE TABLETS 100mg
Clozapine 100mg

Product Name
Zapine Tablets 100mg

Product Description
It is a pale-yellow, round, bevel-edge flat tablet, with a line scored on one side and a ST 364 on the other side.

Composition
Each tablet contains 100mg of Clozapine.

Mode of Action
Zapine has been shown to be an antipsychotic agent that is different from classical neuroleptics.

In pharmacological experiments, clozapine does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It 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, in addition to potent anti-α-andrenergic, anticholinergic, antihistaminic and arousal reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinically, Zapine produces rapid and marked sedation, and exerts strong antipsychotic effects. It is of particular interest that the latter have been observed in schizophrenic patients resistant to other drug treatment. In such cases, Zapine has proven effective in relieving both positive and negative schizophrenic symptoms. Clinically relevant improvement has been observed in about $^1/_3$ of patients within the first 6 weeks of treatment and in about 60% of patients in whom treatment was continued for up to 12 months. In addition, improvement in some aspects of cognitive dysfunction has been described. Also epidemiological studies showed an approximately 7-fold decrease in suicide and suicide attempts in patients treated with Zapine, compared to schizophrenics not on Zapine.

Pharmacodynamics
Zapine is unique in that it produces virtually no major extrapyramidal reactions eg, acute dystonia; parkinsonian-like side effects and akathisia are rare. In contrast to classical neuroleptics, Zapine produces little or no prolactin elevation, thus avoiding adverse effects eg, gynaecomastia, amenorrhoea, galactorrhoea and impotence.

A potentially serious adverse reaction caused by Zapine therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7%, respectively. In view of this risk, the use of Zapine should be limited to patients who are treatment-resistant (see Indications) and in whom regular haematological examinations can be performed (see Precautions and Side Effects).

Pharmacokinetics
The absorption of orally administered Zapine is 90-95%; neither rate nor extent of absorption is influenced by food.

Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50-60%. In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hrs (range: 0.4-4.2 hrs), and the volume of distribution is 1.6 L/kg. Clozapine is approximately 95% bound to plasma proteins. Its elimination is biphasic, with a mean terminal half-life of 12 hrs (range: 6-26 hrs).

After single doses of 75 mg, the mean terminal half-life was 7.9 hrs; it increased to 14.2 hrs when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days. Dosage increases from 37.5-75 mg and 150 mg given twice daily were found to result during steady-state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.

Clozapine is almost completely metabolised before excretion. Of the main metabolites, only the demethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration. Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the faeces.

Indications
Treatment with clozapine is indicated in treatment-resistant schizophrenic patients only, i.e. schizophrenic patients who are non-responsive to or intolerant of classic neuroleptics.

Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed neuroleptics prescribed for adequate durations.

Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic neuroleptic drugs because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

Recommended Dosage
The dosage must be adjusted individually.
For each patient the lowest effective dose should be used.
Dose adjustment is indicated in patients receiving drugs interacting with clozapine, such as benzodiazepines, or selective serotonin re-uptake inhibitors.
The following dosages for oral administration are recommended:

Starting therapy
12.5 mg (½ of a 25-mg tablet) once or twice on the 1st day, followed by one or two 25-mg tablets on the 2nd day.
If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks.

Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals.

Use in the elderly
It is recommended to initiate treatment at a particularly low dose (12.5 mg given once on the 1st day) and to restrict subsequent dose increments to 25 mg/day.

Therapeutic dose range
In most patients, antipsychotic efficacy can be expected with 300 to 450 mg/day given in divided doses.
Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day.
The total daily dose may be divided unevenly, with the larger portion at bedtime. For maintenance dose, see below.

Maximum dose
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/day. The possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

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 6 months.
If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.

Ending therapy
In the event of planned termination of clozapine therapy, a gradual reduction in dose over a 1- to 2-week period is recommended.
If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting and diarrhoea.

Re-starting therapy
In patients in whom the interval since the last dose of clozapine exceeds 2 days, treatment should be re-initiated with 12.5 mg (½ of a 25-mg tablet) given once or twice on the 1st day.
If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment.
However, in 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, re-titration should be done with extreme caution.

Switching from a previous neuroleptic therapy to clozapine
When clozapine therapy is to be initiated in a patient undergoing oral neuroleptic therapy, it is recommended that the other neuroleptic should first be discontinued by tapering the dosage downwards over a period of approximately 1 week.
Once the neuroleptic has been completely discontinued for at least 24 hours, clozapine treatment can be started as described above.

It is generally recommended that clozapine should not be used in combination with other neuroleptics.

Mode of Administration
Zapine is administered by oral

Contraindications
Previous hypersensitivity to clozapine or any other components of Zapine (see Description). History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy). Impaired bone marrow function. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Circulatory collapse and/or CNS depression of any cause. Severe renal or cardiac disorders (eg, myocarditis). Active liver disease associated with nausea, anorexia or jaundice, progressive liver disease, hepatic failure.

Warnings and Precautions
Warning
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.
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 this confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood.
However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related events in patients treated with the atypical antipsychotics.
Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics 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.

Agranulocytosis
Because of the significant risk of agranulocytosis, a potentially life-threatening adverse 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 4 weeks after discontinuation of treatment.
Clozapine is available only through a distribution system that ensures monitoring of wbc count and anc according to the schedule described below prior to delivery of the next supply of medication.

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 dose. 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 post-marketing safety databases suggest that Clozapine is associated with an increased risk of total myocarditis, especially during, but not limit to, the first month of therapy. In patients is 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., 2 or more days since the last dose, treatment should be started with 12.5mg once or twice daily.
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.

Precautions
Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an

acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically reevaluated. Although it is not known whether the risk would be increased, it is prudent to either avoid Clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Withdrawal
On planned withdrawal reduce dose over 1-2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary observe patient carefully.

Agranulocytosis
Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor counts every week for 18 weeks then at least every 2 weeks and if Clozapine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm³ or if absolute neutrophil count below 1500/mm³ discontinue permanently and refer to haematologist. Avoid drugs which depress leucopoiesis; patients should report immediately symptoms of injection, especially influenza-like illness.

Myocarditis and cardiomyopathy
Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported. The CSM has advised:

- Physical examination and medical history before starting Clozapine
- Specialist examination if cardiac abnormalities or history of heart disease found – Clozapine initiated only in absence of severe heart disease and if benefit outweighs risk;
- Persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy;
- If myocarditis or cardiomyopathy suspected Clozapine should be stopped and patient evaluated urgently by cardiologist
- Discontinue permanently in clozapine-induced myocarditis or cardiomyopathy

Fever
Clozapine therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of NMS must be considered. There have been several reports of NMS in patients receiving Clozapine, usually in combination with lithium or other CNS-active drugs.

Pulmonary Embolism
The possibility of pulmonary embolism should be considered in patients receiving Clozapine who present with deep-vein thrombosis, acute dyspnea, chest pain, or with other respiratory signs and symptoms.

Deep-vein thrombosis has also been observed in association with Clozapine therapy. Whether pulmonary embolus can be attributed to Clozapine or some characteristic(s) of its users is not clear, but the occurrences of deep-vein thrombosis or respiratory symptomatology should suggest its presence.

Hepatitis
Caution is advised in patients using Clozapine who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and preexisting liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during Clozapine treatment, liver function test should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with Clozapine should be discontinued.

Anticholinergic Toxicity
Eye: Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of narrow-angle glaucoma.

Gastro-intestinal obstruction
Reactions resembling gastro-intestinal obstruction reported. Clozapine should be used cautiously with drugs which cause constipation (e.g. antimuscarinic drugs) or in history of colonic disease or bowel surgery. Monitor for constipation and prescribe laxative if required.

Prostate: Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of prostatic enlargement.

Interference with Cognitive and Motor Performance
Because of initial sedation, Clozapine may impair metal and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual-dose escalation should be carefully adhered to and patients cautioned about activities requiring alertness.

Use in Patients with Concomitant Illness
Clinical experience with Clozapine in patients with concomitant systemic disease is limited. Nevertheless, caution is advisable in using Clozapine in patients with renal or cardiac disease.

Use in Patients Undergoing General Anesthesia
Caution is advised in patients being administered general anesthesia because of the CNS effects of Clozapine. Check with the anesthesiologist regarding continuation of Clozapine therapy in a patient scheduled for surgery.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by Clozapine. Clozapine did not produce

genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

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

Geriatric Use
Clinical studies of Clozapine did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently than younger subjects.
Orthostatic hypotension can occur with Clozapine treatment and tachycardia, which may be sustained, has been observed in about 25% of patients taking Clozapine. Other adverse Cardiovascular and Respiratory Effects. Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.
Also, elderly patients may be particularly susceptible to the anticholinergic effects of Clozapine, such as urinary retention and constipation.
Dose selection for an elderly patient should be cautions, reflecting the greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy. Other reported clinical experience does suggest that the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women.

Interactions with other Medicaments
Interactions with other medicinal products and other forms of interaction: Pharmacodynamic-Related Interactions: Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Zapine (see also Precautions).

Zapine may enhance the central effects of alcohol, MAOIs and CNS depressants eg, narcotics, antihistamines and benzodiazepines.

Particular caution is advised when Zapine therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other psychotropic drug, as these patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest.

Because of the possibility of additive effects, caution is essential in the concomitant administration of drugs possessing anticholinergic, hypotensive or respiratory depressant effects.

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

Owing to its anti-α-adrenergic properties, Zapine may reduce the blood pressure-increasing effect of norepinephrine or other predominantly α-adrenergic agents and reverse the pressure effect of epinephrine.

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and in isolated cases of delirium where Zapine was co-administered with valproic acid

have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Pharmacokinetic-Related Interactions: Clozapine is a substrate for many CYP-450 isoenzymes, particularly 1A2 and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimised. Nevertheless, caution is called for in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of these enzymes.

With tricyclic antidepressants, phenothiazines and type I antiarrhythmics, which are known to bind to cytochrome P-450 2D6, no clinically relevant interactions have been observed.

Concomitant administration of drugs known to induce cytochrome P-450 enzymes may decrease the plasma levels of clozapine: Drugs known to induce the activity of 3A4 and with reported interactions with clozapine include, for instance, carbamazepine, phenytoin, rifampicin.

Known inducers of 1A2 include, for instance, omeprazole and nicotine. In cases of sudden cessation of nicotine abuse, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects. Interactions with omeprazole have not been reported to date.

Concomitant administration of drugs known to inhibit the activity of cytochrome P-450 isoenzymes may increase the plasma levels of clozapine: Drugs known to inhibit the activity of the major isoenzymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4) and fluvoxamine (1A2).

Potent inhibitors of CYP3A eg, azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations. No interactions have been reported to date however the plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period.

Elevated clozapine plasma concentrations also have been reported in patients receiving the drug combination with selective serotonin re-uptake inhibitors (SSRIs) eg, paroxetine (1A2), sertraline or fluoxetine.

Pregnancy and Lactation

Pregnancy:

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the foetus due to clozapine. However, the safe use of Zapine in pregnant women has not been established. Therefore, Zapine should be used in pregnancy only if the expected benefit clearly outweighs any potential risk.

Lactation:
Animal studies suggest that clozapine is excreted in breast milk; therefore, mothers receiving Zapine should not breastfeed.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following 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.

Zapine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Side Effects
Haematological: Development of granulocytopenia and agranulocytosis is a risk inherent to Zapine treatment. Although generally reversible on withdrawal of the drug, agranulocytosis may result in sepsis and can prove fatal. The majority of cases (approximately 85%) occur within the first 18 weeks of treatment. Because immediate withdrawal of the drug is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count (see Precautions) is mandatory.

Unexplained leucocytosis and/or eosinophilia may occur, especially in the initial weeks of treatment. Very rarely, Zapine may cause thrombocytopenia.

Central Nervous System: Fatigue, drowsiness and sedation are among the most common side effects observed. Dizziness or headache may also occur.

Zapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid increase and in patients with preexisting epilepsy. In this case, the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsant drugs, the possibility of a pharmacokinetic interaction should be considered.

In rare cases, Zapine may cause confusion, restlessness, agitation and delirium.

Extrapyramidal symptoms may occur, but are milder and less frequent than those seen during classical neuroleptic treatment. Rigidity, tremor and akathisia have been reported, but acute dystonia is not an established side effect of Zapine treatment.

Very rarely, tardive dyskinesia, has been reported in patients on Zapine, who had been treated with other antipsychotic agents, so that a causal relationship cannot be established. Patients in whom tardive dyskinesia developed with other neuroleptics have improved on Zapine.

Cases of neuroleptic malignant syndrome (NMS) have been reported in patients receiving Zapine, either alone or in combination with lithium or other CNS-active agents.

Autonomic Nervous System: Dry mouth, blurred vision, and disturbances in sweating and temperature regulation have been reported. Hypersalivation is a relatively common side effect.

Cardiovascular System: Tachycardia and postural hypotension, with or without syncope, may occur, especially in the initial weeks of treatment. Less commonly, hypertension may also occur. In rare cases, profound circulatory collapse has been reported (see Precautions and Interactions). ECG changes may occur and isolated cases of cardiac arrhythmias, pericarditis and myocarditis (with or without eosinophilia) have been reported, some of which have been fatal. Therefore, in patients on Zapine in whom tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath, or signs and symptoms of heart failure develop, the diagnosis of myocarditis should be considered and, if confirmed, Zapine should be discontinued. Very rare reports of cardiomyopathy have been received; if cardiomyopathy is diagnosed, Zapine should be discontinued unless the benefit outweighs the risk to the patient. Rare cases of thromboembolism have been reported.

Respiratory System: In isolated cases, with or without circulatory collapse, respiratory depression or arrest has occurred (see Precautions and Interactions). Rarely, aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

Gastrointestinal System: Nausea, vomiting, constipation and very rarely, ileus may occur.

Transient, asymptomatic elevations of liver enzymes and rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, Zapine should be discontinued (see Precautions).

As a rare event, Zapine treatment may be associated with dysphagia, a possible cause of aspiration.

There have also been rare reports of parotid gland enlargement.

In rare cases, acute pancreatitis has been reported.

Genitourinary System: Both urinary incontinence and urinary retention and, in a few cases, priapism have been reported.

Isolated cases of acute intestinal nephritis have been reported in association with Zapine therapy.

Miscellaneous: Benign hyperthermia may occur, especially in the initial weeks of treatment. Isolated reports of skin reactions have been received. On rare occasions, severe

hyperglycaemia sometimes leading to ketoacidosis/hyperosmolar coma, has been reported in patients on Zapine treatment with no prior history of hyperglycaemia (see Precautions).

Rarely, increases in CPK values have occurred. With prolonged treatment, considerable weight gain has been observed in some patients. Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Isolated cases of such deaths have been reported in patients receiving Zapine.

Symptoms and Treatment of Overdose
In cases of acute intentional or accidental Zapine overdosage, for which information on the outcome is available, to date the mortality is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses >2000 mg. There have been reports of patients recovering from an overdose in excess of 10,000 mg.

However, in a few adult individuals, primarily those not previously exposed to Zapine, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and in one case, to death. In young children, the intake of 50-200 mg resulted in strong sedation or coma, without being lethal.

Symptoms:
Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia; convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment:
Gastric lavage and/or the administration of activated charcoal within the first 6 hrs after the ingestion of the drug. (Peritoneal dialysis and haemodialysis are unlikely to be effective.) 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.

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

Presentation
10 tablets in PVC/foil blister strip. 10 strips or 5 strips are packed in a folded paper box.

Storage Conditions
Store at temperature below 30°C

Shelf-life
This product can be used within 36 months from the date of manufacture if kept as recommended.

Registration Number
Zapine Tablets 100mg – MAL07090952AZ

Name and Address of Manufacturer
Taiwan Biotech Co., Ltd
22, Chieh Shou Road, Taoyuan
Taiwan., R.O.C
Tel : +886 3 36121316
Fax : +886 3 3614294

Product Registration Holder
Averroes Pharmaceuticals Sdn. Bhd.
03-08-01 & 03-09-01, Block 3, Presint Alami
Worldwide Business Center II
Persiaran Akuatik, Seksyen 13
40100 Shah Alam, Selangor
Malaysia
Tel : +603 55111433
Fax: +603 55111431

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