CLOZAPINE

ZIPROC - 25
ZIPROC - 100
25 mg and 100 mg Tablet
ANTIPSYCHOTIC

FORMULATION
Each tablet contains:
Clozapine ..... 25 mg and 100 mg

PRODUCT DESCRIPTION
Clozapine (Ziproc-25) 25 mg Tablet and Clozapine (Ziproc-100) 100 mg Tablet are light yellow coloured, round, binconvex, uncoated tablet with bisecting line on one side.

CLINICAL PHARMACOLOGY
Clozapine is classified as an atypical antipsychotic agent, which differs from conventional antipsychotics. It has a weak dopamine receptor blocking activity at D2 receptors, but has a D1 anti-adrenergic, anticholinergic, antihistaminergic and arousal reaction inhibiting effects. It has also been shown to possess antiserotonergic property. Clozapine produces rapid and marked sedation and exerts strong antipsychotic effects. It is effective in patients exhibiting both positive and negative schizophrenic symptoms.

PHARMACOKINETICS
Although clozapine is well absorbed from the gastrointestinal tract, its bioavailability is limited to about 50% by fisrt-pass metabolism. Peak plasma concentrations are achieved an average of about 2.5 hours after oral administration. Clozapine is about 95% bound to plasma proteins and has mean terminal elimination half-life of about 12 hours at a steady state. It is almost completely metabolized and routes of metabolism include N-demethylation, hydroxylation, and N-oxidation, the desmethyl metabolite (norclozapine) has limited activity. The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Metabolites and trace amounts of unchanged drug are excreted mainly in the urine and also in the feces. There is wide interindividual variation in plasma concentrations of clozapine and no simple correlation has been found between plasma concentrations and therapeutic effect.

INDICATIONS
Used for the management of schizophrenia; reserved for patients who fail to respond to or who experience severe extrapyramidal side-effects with classical antipsychotics.
Used for reducing the risk of recurrent suicidal behavior in those with schizophrenia or schizoaffective disorder who at risk of suicidal behavior.
Also used in the management of treatment-resistant psychoses associated with parkinson's disease.

DOSAGE AND ADMINISTRATION
To minimize the incidence of adverse effects, clozapine therapy should be introduced gradually, beginning with low doses and increasing according to response.

Schizophrenia including reducing the risk of suicidal behavior
Usual Dose: 12.5 mg (half a 25 mg tablet) once or twice on the first day followed 25 mg or twice on the second day. Thereafter the daily dose may be increased gradually in increments of 25 to 50 mg to achieve a daily dose of up to 300 mg within 2 to 3 weeks. Subsequent increments of 50 to 100 mg may be made once or twice weekly.
Therapeutic Dose: Most patients respond to 200 to 450 mg daily in divided doses.
Maximum Dose: Daily maximum dose of 900 mg/ day should not be exceeded and should be given in divided doses.
Maintenance Dose: Once a therapeutic response has been obtained, a gradual reduction of dosage to a suitable maintenance dose may be possible. Daily maintenance dose of 200 mg or less may given as single dose in the evening.
Ending Therapy: If clozapine is to be withdrawn this should be done gradually over a 1 to 2 week period. However, immediate discontinuation with careful observation is essential if neutropenia develops or if myocarditis is suspected.

Psychoses in Parkinson's Disease
Initial Dose: Not more than 12.5 mg (half a 25 mg tablet) once daily in th evening. Subsequent increases may be made in increments of 12.5 mg, with up to 2 increases each week, a dose of 50 mg daily should not be reached before the end of the second week.
Therapeutic Dose: The usual dose ranges from 25 to 37.5 mg daily although some patients may require higher doses. Increases above 50 mg should be made at weekly intervals.
Maximum Dose: Maximum dose of 100 mg daily.
Maintenance Dose: The dose of clozapine may need to be adjusted if psychotic symptoms recur following increases in antiparkisonian therapy: the dose may be increased in weekly increments of 12.5 mg to a maximum of 100 mg daily, as a single dose or in two divided doses.
Ending Therapy: Planned withdrawal cloazpine should be gradual, in decrements of 12.5 mg over 1 to 2 weeks, in patients with Parkinson's disease.
Or as prescribed by the physician.

CONTRAINDICATIONS
Clozapine should not be given to patients with uncontrolled epilepsy, alcoholic or toxic psychoses, drug intoxication, or a history or circulatory collapse. It is contraindicated in patients with bone-marrow suppression, myeloproliferative disorders, or any abnormalities of white blood cell count or differential count. It is also contraindicated in patients with history of drug-induced neutropenia or agranulocytosis with a exception of that due to chemotherapy. It should not be used with drugs that carry a high risk of bone-marrow suppression. Clozapine is contraindicated in patients with severe renal impairment caution is required in mild to moderate renal impairment. It should be used with caution in hepatic impairment and avoided in symptomatic or progressive liver disease or hepatic failure. Contraindicated in patients with history of cardiac impairment. Clozapine is contraindicated in patients cardiac failure, paralytic ileus.

WARNING AND PRECAUTIONS
Clozapine can cause agranulocytosis.
Monitoring of white blood cell and absolute neutrophil count is mandatory during treatment. A white blood cell count and a differential blood count must be performed before starting clozapine therapy and regularly throughout the treatment. Treatment should not be started is the white blood cell count is less than 3500 cells/nm^3 and the absolute neutrophil count (ANC) is less than 2000 cells/nm^3, or there is an abnormal differential count. Monitoring should continue throughout therapy and 4 weeks after discontinuation.
If during therapy the white blood cell count falls to 3000 and 3500 cells/nm^3 or the ANC falls between 1500 and 2000 cells/nm^3 the monitoring should be performed twice weekly until the value stabilize or increase.
Clozapine should be withdrawn immediately if the white blood cell count falls below 3000 cells/nm^3 or the ANC drops below 1500 cells/nm^3, counts should be monitored daily until they return to normal. Clozapine should not be restarted with these patients.
Patients or their carers should report the development of any infection or signs such as fever, sore throat, or flu-like symptoms which suggest infection.
If treatment with clozapine is interrupted for reasons other than abnormal hemotalogical values then more frequent monitoring may be required. Patients who have taken clozapine for at least 18 weeks and stop therapy for more than 3 days but not less than 4 weeks should resume weekly monitoring for the next 6 weeks before reducing to at least every 4 weeks if the counts are stable; a break of 4 weeks or more would require weekly monitoring for the next 18 weeks.
Clozapine should be withdrawn if the eosinphil count is greater than 3000 cells/nm^3; it should only be restarted once the count has fallen to below 1000 cells/nm^3.
Discontinuation of clozapine is recommended if the platelet count falls below 50000/nm^3.
Because of an increased risk of collapse due to orthostatic hypotension associated with initial titration of dosage of cloazpine it is recommended that treatment should be initiated under close medical supervision. In addition, patients with parkinson's disease should have their blood pressure monitored for the first two weeks of treatment.
Patients who develop tachycardia at rest, dyspnea, or signs and symptoms of heart failure should be investigated immediately and clozapine treatment should be discontinued is a diagnosis of myocarditis is suspected.
Clinical monitoring for hyperglycemia has been recommended, especially in patients with or at risk of developing diabetes.

On planned withdrawal the dose of clozapine should be reduced gradually over at least 1 to 2 week period in order to avoid the risk of rebound psychosis. If abrupt withdrawal is necessary then patients should be observed carefully. Clozapine may affect the performance of skilled tasks such as driving.

PREGNANCY AND LACTATION

The safe use of Clozapine in pregnancy has not been established and its use is not recommended. Animal studies suggest that Clozapine is excreted in breast milk, therefore, mothers receiving Clozapine must not breast feed.

DRUG INTERACTIONS

Clozapine may enhance the central effects of CNS depressants including alcohol, benzodiazepines and MAOIs.

Clozapine should not be used concurrently with drugs which carry a high risk of bone-marrow suppression including carbamazpine, co-trimoxazole, chloramphenicol , penicillamine, sulfonamides, antineoplastics or pyrazolone analgesics such as azapropazone. Long-acting depot antipsychotics should not be used with clozapine as they cannot be withdrawn rapidly when neutropenia occur. Additive effects may occur when clozapine is given with drugs that possesses antimuscarnic, hypotensive, or respiratory depressant effects. Clozapine may reduce the effects of alpha-adrenoceptor agonists such as noradrenaline. The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Concomitant use of drugs that inhibit or act as a substrate to this isoenzyme may affect plasma concentrations of clozapine and the dose of clozapine may need to be altered. Increased plasma-clozapine concentrations, with an increased risk of adverse effects, may be seen in patients who suddenly stop smoking. Use with phenytoin or other enzyme-inducing drugs may accelerate the metabolism of clozapine and reduce its plasma concentrations.

ADVERSE DRUG REACTIONS

Although clozapine may share some of the adverse effects seen the classical antipsychotics, the incidence and severity of such effects may vary; antimuscarinic effects with clozapine may be more pronounced. Sedation and weight gain may also be more prominent. Clozapine can cause reversible neutropenia which may progress to a potentially fatal agranulocytosis; strict monitoring of white blood cell counts is essential. Eosinophilia may also occur.

Extrapyramidal disorders, including tardive dyskinesia appear to be rare with clozapine. Clozapine has a little effect on prolactin secretion. Clozapine appears to have a greater epileptic potential than chlorpromazine but a comparable risk of cardiovascular effects such as tachycardia and orthostatic hypotension. In rare cases circulatory collapse with cardiac and respiratory arrest has occurred, and hypertension has also been reported. Clozapine is also associated with an increased risk developing myocarditis that may, in rare cases, be fatal; cardiomyopathy and pericarditis have also been reported.

Additional side-effects of clozapine include dizziness, hypesalivation (particularly at night), headache, nausea, vomiting, constipation (which in few cases has led to gastro-intestinal obstruction and paralytic ileus), urinary incontinence and retention, anxiety, confusion, fatigue, and transient fever which may be distinguished from signs of impending agranulocytosis. There have been also rare reports of dysphagia, paratid gland enlargement, delirium, thromboembolism, acute pancreatitis, hepatitis and cholestatic jaundice, and very rarely fulminant hepatic necrosis. Isolated cases of acute interstitial nephritis have been reported. Abnormalities of glucose hemeostatis and the onset of diabetes mellitus occur uncommonly; severe hyperglycemia, sometimes leading to ketoacidosis ahs been reported rarely. Many of the adverse effects of clozapine are most common at the beginning of therapy and may be minimized by gradual increase in dosage.

“For Suspected Adverse Reaction, report to FDA: www.fda.gov.ph or to Torrent: www.torrentpharma.com”.

Patient must seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT

Symptoms of overdosage are drowsiness, lethargy, coma, areflexia,confusion, agitation, hyperflexia, delirium, convulsions, hypersalivation, mydriasis, blurred vision, thermolability, tachycardia, hypotension, collapse, cardiac arrhythmia and respiratory depression. Management of overdosage include gastric lavage followed by administration of activated charcoal, symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, control of electrolytes and acid base balance. The use of adrenaline and its derivative should be avoided for treatment of hypotension because of possibility of "reverse adrenaline" effect. Close medical supervision is necessary for at least four days because of possibility of delayed reactions.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

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

AVAILABILITY

Clozapine (Ziproc-25) 25 mg Tablet - Alu/PVC Blister Pack x 10’s (Box of 100’s) - DRP - 3291

Clozapine (Ziproc-100) 100 mg Tablet - Alu/PVC Blister Pack x 10’s (Box of 100’s) - DRP - 3289

Date of First Authorization

January 13, 2006

Date of Revision

January 2018

torrent PHARMA

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