Zacloz 25mg 100mg

(Clozapine)

Tablets U.S.P.

زیکلوز ۲۵ ملی گرام ۱۰۰ ملی گرام

(کلوزاپین) ٹیبلٹس یو۔ایس۔پی۔

QUALITATIVE AND QUANTITATIVE COMPOSITION

Zacloz Tablet U.S.P. 25mg: Each tablet contains:
Clozapine U.S.P. 25mg
Zacloz Tablet U.S.P. 100mg: Each tablet contains:
Clozapine U.S.P. 100mg

WARNING: WARNING: SEVERE NEUTROPENIA; ORTHOSTATIC HYPOTENSION, BRADYCARDIA, AND SYNCOPE; SEIZURE; MYOCARDITIS AND CARDIOMYOPATHY; INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA¬RELATED PSYCHOSIS
(1) Severe Neutropenia: CLOZAPINE can cause severe neutropenia, which can lead to serious and fatal infections. Patients initiating and continuing treatment with CLOZAPINE must have a baseline blood absolute neutrophil count (ANC) measured before treatment initiation and regular ANC monitoring during treatment. (2) CLOZAPINE is available only through a restricted program called the Clozapine REMS. (3) Orthostatic Hypotension, Bradycardia, and Syncope: Risk is dose-related. Starting dose is 12.5 mg. Titrate gradually and use divided dosages. (4) Seizure: Risk is dose-related. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors for seizure. (5) Myocarditis, Cardiomyopathy and Mitral Valve Incompetence: Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions. (6) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: CLOZAPINE is not approved for this condition.

DESCRIPTION

Clozapine, an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4¬methyl-1-piperazinyl)-5H-dibenzo [b,e] [1,4] diazepine.

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¬HT2A) 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.

Pharmacokinetics:

Absorption: In humans, 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 to 12 hours), compared to a mean elimination half-life of 12 hours (range: 4 to 66 hours), after achieving steady state with 100 mg twice daily dosing.

INDICATIONS AND USAGE

Treatment-Resistant Schizophrenia: CLOZAPINE is indicated for the treatment of severely ill patients with schizophrenia who fail to respond adequately to standard antipsychotic treatment. Because of the risks of severe neutropenia and of seizure associated with its use, CLOZAPINE should be used only in patients who have failed to respond adequately to standard antipsychotic treatment. Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorder CLOZAPINE is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state.

CONTRAINDICATIONS

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

INTERACTIONS

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 inhi-bi-tors. 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 co-administered enzyme inducers; because discontinuation of inducers can result in increased clozapine plasma levels and an increased risk of adverse reactions.

Anticholinergic Drugs: Concomitant treatment with clozapine and other drugs with anticholinergic activity (e.g., benztropine, cyclobenzaprine, diphenhydramine) can increase the risk for anticholinergic toxicity and severe gastrointestinal adverse reactions related to hypomotility. Avoid concomitant use of CLOZAPINE with anticholinergic drugs when possible. **Drugs that Cause QT Interval Prolongation:** Use caution when administering concomitant medications that prolong the QT interval or inhibit the metabolism of clozapine. **Potential for CLOZAPINE to Affect Other Drugs:** Concomitant use of CLOZAPINE with other drugs metabolized by CYP2D6 can increase levels of these CYP2D6 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 POPULATION

Pregnancy Category B: There are no adequate or well-controlled studies of clozapine in pregnant women. **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.

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. **Hospice Patients**: For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver. Individual treatment decisions should weigh the importance of monitoring ANC in the context of the need to control psychiatric symptoms and the patient's terminal illness.

ADVERS EVENTS AND PRECAUTIONS

Gastrointestinal Hypomotility with Severe Complications: Severe gastrointestinal adverse reactions have occurred with the use of CLOZAPINE. If constipation is identified, close monitoring and prompt treatment is advised. **Eosinophil-**

ia: Assess for organ involvement (e.g., myocarditis, pancreatitis, hepatitis, colitis, nephritis). Discontinue if these occur. **QT Interval Prolongation:** Can be fatal. Consider additional risk factors for prolonged QT interval (disorders and drugs). **Hyperglycemia and Diabetes Mellitus:** Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. **Dyslipidemia:** Undesirable alterations in lipids have occurred in patients treated with atypical antipsychotics. **Weight Gain:** Significant weight gain has occurred. Monitor weight gain. **Neuroleptic Malignant Syndrome (NMS):** Immediately discontinue and monitor closely. Assess for comorbid conditions. **Hepatotoxicity:** Can be fatal. Monitor for hepatotoxicity. Discontinue treatment if hepatitis or transaminase elevations combined with other symptoms occur. **Fever:** Evaluate for infection and for neutropenia, NMS. **Pulmonary Embolism (PE):** Consider PE if respiratory distress, chest pain, or deep-vein thrombosis occur. **Anticholinergic Toxicity:** When possible, avoid use with other anticholinergic drugs and use with caution in patients with a current diagnosis or prior history of constipation, urinary retention, clinically significant prostatic hypertrophy, or other conditions in which anticholinergic effects can lead to significant adverse reactions. **Interference with Cognitive and Motor Performance:** Advise caution when operating machinery, including automobiles.

DOSAGE AND ADMINISTRATION

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, patients responding to CLOZAPINE should continue maintenance treatment on their effective dose beyond the acute episode. **Discontinuation of Treatment:** Method of treatment discontinuation will vary depending on the patient's last ANC:

• Appropriate ANC monitoring based on the level of neutropenia if abrupt treatment discontinuation is necessary because of moderate to severe neutropenia. • Reduce the dose gradually over a period of 1 to 2 weeks if termination of CLOZAPINE therapy is planned and there is no evidence of moderate to severe neutropenia. • For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for general population patients until their ANC is ≥1500/μL and for BEN patients until their ANC is ≥1000/μL or above their baseline.

• Additional ANC monitoring is required for any patient reporting onset of fever (temperature of 38.5°C or 101.3°F, or greater) during the 2 weeks after discontinuation. • Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea. **Re-Initiation of Treatment:** When restarting CLOZAPINE 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).

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

Management of Overdosage

There is no available specific antidote to an overdose of CLOZAPINE. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Monitor cardiac status and vital signs. Use general symptomatic and supportive measures. Consider the possibility of multiple-drug involvement.

INSTRUCTIONS

Dosage as directed by the physician.
Store at 20°C - 25°C, excursions permitted to 15°C - 30°C.
Protect from heat, light & moisture.
Keep all medicines out of the reach of children.

PRESENTATION

Zacloz Tablet 25mg: Available in Alu/Alu Blister of 5x10's with leaf insert. **Zacloz Tablet 100mg:** Available in Alu/Alu Blister of 5x10's with leaf insert.

ہدایات: خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۲۰ سے ۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

For detailed information:

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