(clozapine)
25 mg or 100 mg tablets

Important note:
Before prescribing, consult full prescribing information.

Presentation:
Clozapine. Tablets containing 25 mg or 100 mg of clozapine. The scored tablets can be divided into equal halves (the formulation may differ in some countries).

Indications:
♦ Schizophrenia in patients who are non-responsive to or intolerant to classic antipsychotics.
♦ Recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorders.
♦ Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

Dosage:
♦ Schizophrenia and recurrent suicidal behaviour: 12.5 mg (half a 25 mg tablet) once or twice on the first day, 25 or 50 mg on the second day, followed by stepwise dosage increases up to 300-450 mg (in some patients 600 mg) per day in divided doses. Maximum oral dose: 900 mg/day. For maintenance treatment lower doses may suffice.
♦ Psychotic disorders during the course of Parkinson's disease: Starting dose must not exceed 12.5 mg per day (half a 25 mg tablet), taken in the evening, followed by subsequent dose increase of 12.5 mg increments with a maximum of two increments a week up to a maximum of 50 mg. Mean effective dose is between 25 and 37.5 mg per day, preferably given as a single dose in the evening. Maximum dose: 50 mg per day, to be exceeded only in exceptional cases. Dose of 100 mg per day must never be exceeded.

Special patients population:
♦ In patients with cardiovascular disorders or mild to moderate renal impairment the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.
♦ In patients 60 years and older the initial recommended dose is 12.5 mg given once on the first day with subsequent dose increments restricted to 25 mg/day.

Contraindications:
♦ Known hypersensitivity to clozapine or excipients of Leponex®/Clozaril®.
♦ Patients 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.
♦ Uncontrolled epilepsy.
♦ Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
♦ Circulatory collapse.
♦ CNS depression.
♦ Severe renal or cardiac disorders (e.g. myocarditis).
♦ Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
♦ Paralytic ileus.

Warnings/Precautions:
♦ Leponex/Clozaril can cause agranulocytosis. Its use should be limited to patients with treatment-resistant schizophrenia or patients with schizophrenia or schizoaffective disorder who are at risk for re-experiencing suicidal behaviour, who have normal leukocyte findings, and in whom the mandatory white blood cell counts and absolute neutrophil counts (weekly during the first 18 weeks, at least monthly thereafter) can be performed.
♦ Concomitant use of drugs with a substantial potential to depress bone marrow function and of long-acting depot antipsychotics should be avoided. For instructions on how to proceed in the management of these situations, consult the prescribing information.
event of infection and/or granulocytopenia, see full product information.

♦ Caution is recommended if eosinophilia or thrombocytopenia develop.

♦ Caution is recommended in the presence of cardiovascular disorders (in particular if tachycardia persists at rest, possibly accompanied by arrhythmias, shortness of breath, or signs and symptoms of heart failure).

♦ Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson’s disease.

♦ Myocardial infarction which may be fatal has been reported in postmarketing experience.

♦ Risk of QT prolongation with atypical antipsychotics. Caution is recommended in patients with family history of QT prolongation or when prescribed with medicines known to prolong the QTc interval.

♦ Caution is recommended in patients with risk factors for stroke.

♦ Immobilisation of patients should be avoided due to risk of thromboembolism from potential sedation and weight gain.

♦ Risk of metabolic changes with atypical antipsychotics. Caution is recommended in the presence of diabetes or if symptoms of hyperglycaemia develop. Clinical monitoring of glucose, lipids, and weight is recommended.

♦ Leponex/Clozaril may lower seizure threshold. Caution is recommended in patients with a history of seizures.

♦ Caution is recommended in the presence of prostatic enlargement, narrow-angle glaucoma, and chronic constipation.

♦ Carefully evaluate patients with high fever to rule out the possibility of an underlying infection, the development of agranulocytosis, or the possibility of neuroleptic malignant syndrome (NMS). If NMS is confirmed, discontinue Leponex/Clozaril immediately and administer appropriate medical measures.

♦ Caution is recommended if symptoms of liver dysfunction develop.

♦ Caution is recommended in the presence of renal disorders.

♦ Caution is recommended in children, adolescents, and patients aged 60 years and older.

♦ If treatment is discontinued abruptly, the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound.

**Pregnancy:**
Use in pregnancy is not recommended unless potential benefits outweigh the potential risks.

**Breast-feeding:**
Breast-feeding should be avoided during treatment.

**Driving and using machines:**
Caution is recommended when patients drive a vehicle or operate machinery.

**Interactions:**
Alcohol, MAO inhibitors, CNS depressants, narcotics, antihistamines, benzodiazepines, anticholinergic agents, antihypertensive agents, adrenaline, substances with respiratory depressant effects, valproic acid, omeprazole, cimetidine, erythromycin, rifampicin, phenytoin, carbamazepine, selective serotonin re-uptake inhibitors, fluvoxamine, ciprofloxacin, lithium, azole antymycotics, protease inhibitors, caffeine intake, nicotine abuse.

**Adverse reactions:**

♦ Very common (>10%): drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation;

♦ Common (1 to 10%): leukopenia/decreased WBC/neutropenia, eosinophilia, leucocytosis, weight gain, dysarthria, seizures/convulsions/myoclonic jerks, extrapyramidal symptoms, akathisia, tremor, rigidity, headache, blurred vision, ECG changes, syncope, postural hypotension, hypertension, nausea, vomiting, dry mouth, elevated liver enzymes, urinary retention, urinary incontinence, benign hyperthermia, disturbances in sweating/temperature regulation, fatigue;

♦ Uncommon (0.1 to 1%): agranulocytosis, dysphoria, neuroleptic malignant syndrome;

♦ Rare (0.01 to 0.1%): anaemia, diabetes aggravated, impaired glucose tolerance, new onset diabetes, restless legs, agitation, confusion, delirium, circulatory collapse, arrhythmias, myocarditis, pericarditis, thromboembolism, aspiration of
ingested food, pneumonia and lower respiratory tract infection which may be fatal, dysphagia, pancreatitis, hepatitis, cholestatic jaundice, increased CPK;

♦ **Very rare (<0.01%):** thrombocytopenia, thrombocythemia, hyperosmolar coma, ketoacidosis, severe hyperglycaemia, hypercholesterolemia, hypertriglyceridaemia, tardive dyskinesia, obsessive compulsive symptoms, cardiomyopathy, respiratory depression or arrest, parotid gland enlargement, intestinal obstruction/ileus/faecal impaction, fulminant hepatic necrosis, skin reactions, interstitial nephritis, priapism, sudden unexplained death;

♦ **Not known:** cholinergic syndrome, EEG changes, myocardial infarction which may be fatal, chest pain/angina pectoris, nasal congestion, diarrhea, abdominal discomfort/heartburn/dyspepsia, hepatic steatosis, hepatic necrosis, hepatotoxicity, hepatic fibrosis, hepatic cirrhosis, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant; muscle weakness, muscle spasms, muscle pain, renal failure;

♦ **No conclusive causal relationship:** ventricular tachycardia, QT prolongation with torsades de pointes, cardiac arrest.

**Packs and prices:** Country specific.

**Legal classification:** Country specific.