NOVARTIS

Leponex can cause agranulocytosis. Its use should be limited to patients:
- **with schizophrenia who are non-responsive to or intolerant of classical antipsychotic agents, or with schizophrenia or schizoaffective disorder who are at risk of recurrent suicidal behavior (see section INDICATIONS)**
- **who have initially normal leukocyte findings (white blood cell count (WBC) ≥ 3500/mm^3 (≥3.5 x 10^9/L), and absolute neutrophil counts (ANC) ≥ 2000/mm^3 (≥2.0 x 10^9/L)),**
- **and in whom regular white blood cell counts and absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Leponex (see section WARNINGS AND PRECAUTIONS).**

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving Leponex should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia (see section WARNINGS AND PRECAUTIONS).
Leponex must be dispensed under strict medical supervision in accordance with official recommendations (see section WARNINGS AND PRECAUTIONS).

Leponex®

Antipsychotic agent

DESCRIPTION AND COMPOSITION

25 mg Tablet: Each tablet contains 25 mg clozapine.
100 mg Tablet: Each tablet contains 100 mg clozapine.

Pharmaceutical form

Tablets. The scored tablets can be divided into equal halves.

Active substance

Clozapine
Certain dosage strengths may not be available in all countries.

Active moiety

Clozapine

Excipients

Leponex tablets: magnesium stearate; silica, colloidal anhydrous; povidone, talc; maize starch; lactose monohydrate.
Pharmaceutical formulations may vary between countries.

INDICATIONS

- **Treatment-resistant schizophrenia**

Leponex is indicated in patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.
Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations.
Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

- **Risk of recurrent suicidal behavior**

Leponex 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. Suicidal behavior refers to actions by a patient that put him/herself at high risk for death.

DOSAGE AND ADMINISTRATION

Dosage Information

The dosage must be adjusted individually. For each patient the lowest effective dose should be used. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.
Initiation of Leponex treatment must be restricted to those patients with a WBC count ≥3500/mm^3 (3.5 x 10^9/L) and an ANC ≥2000/mm^3 (2.0 x 10^9/L), and within standardized normal limits.
Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section INTERACTIONS).

Method of Administration

Leponex is administered orally.

Switching from a previous antipsychotic therapy to Leponex

It is generally recommended that Leponex should not be used in combination with other antipsychotics. When Leponex therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the dosage of other antipsychotics be reduced or discontinued by gradually tapering it downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to discontinue the other antipsychotic therapy before initiating treatment with Leponex.

Treatment resistant schizophrenia

Starting therapy

Leponex should be started with 12.5 mg (half a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second 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.

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 being taken at bedtime.

Maximum dose

To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day. However, 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 Leponex 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 (see section WARNINGS AND PRECAUTIONS).

Restarting therapy

In patients in whom the interval since the last dose of Leponex exceeds 2 days, treatment should be re-initiated with 12.5 mg (half a 25-mg tablet) given once or twice on the first 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 (see section WARNINGS AND PRECAUTIONS), but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Reducing the risk of suicidal behavior in schizophrenia and schizoaffective disorder

The dosage and administration recommendations described in the preceding section (DOSAGE AND ADMINISTRATION) regarding the use of Leponex in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behaviour.
A course of treatment with Leponex of at least two years is recommended in order to maintain the reduction of risk for suicidal behaviour. It is recommended that the patient's risk of suicidal behaviour be reassessed after two years of treatment and that thereafter the decision to continue treatment with Leponex be re-visited at regular intervals, based on thorough assessments of patient's risk for suicidal behaviour during treatment.

Special populations

Cardiovascular disorders

In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Renal impairment

In patients with 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.

Hepatic impairment

Patients with hepatic impairment should receive Leponex with caution along with regular monitoring of liver function tests (see section WARNINGS AND PRECAUTIONS)

Pediatrics

No pediatric studies have been performed. The safety and efficacy of Leponex in children and adolescents have not been established.

Patients 60 years of age and older

It is recommended that treatment in patients 60 years and older is initiated at a particularly low dose (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

CONTRAINDICATIONS

- Known hypersensitivity to clozapine or to any of the excipients of Leponex.
- 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 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.
- Paralytic ileus.

WARNINGS AND PRECAUTIONS

Special precautionary measure

Agranulocytosis

Because of the association of Leponex with agranulocytosis, the following precautionary measures are mandatory:
- Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Leponex. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because of the impossibility of removing these medications, which may be potentially myelosuppressive, from the body rapidly in situations where this may be required, e.g. granulocytopenia.
- Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting Leponex.
- Patients who have low white blood cell (WBC) counts because of benign ethnic neutropenia should be given special consideration and may be started on Leponex after agreement of a haematologist.

Leponex must be dispensed under strict medical supervision in accordance with official recommendations.

White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring

White blood cell count (WBC) and differential blood counts must be performed within 10 days prior to starting Leponex treatment to ensure that only patients with normal leukocyte (WBC ≥ 3500/mm^3 (≥ 3.5 x 10^9/L)) and absolute neutrophil counts (ANC ≥2000/mm^3 (≥ 2.0 x 10^9/L)) will receive Leponex. After the start of Leponex treatment, regular WBC count and ANC must be performed and monitored weekly for 18 weeks and thereafter at least every four weeks throughout treatment and for 4 weeks after complete discontinuation of Leponex.
Prescribing physicians should comply fully with the required safety measures. At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. A differential blood count must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count and/or ANC

If during the first 18 weeks of Leponex therapy, the WBC count falls to between 3500/mm^3 and 3000/mm^3 and/or the ANC falls to between 2000/mm^3 and 1500/mm^3, haematological evaluations must be performed at least twice weekly.
After 18 weeks of Leponex therapy, haematological evaluations should be performed at least twice weekly if the WBC count falls to between 3000/mm^3 and 2500/mm^3 and/or the ANC falls to between 1500/mm^3 and 1000/mm^3.
In addition, if, during Leponex therapy, the WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be performed. A substantial drop is defined as a single drop of 3000 mm^3 or more in the WBC count or a cumulative drop of 3000 mm^3 or more within three weeks.
Immediate discontinuation of Leponex is mandatory if the WBC count is less than 3000/mm^3 or the ANC is less than 1500/mm^3 during the first 18 weeks of therapy, or if the WBC count is less than 2500/mm^3 or the ANC is less than 1000/mm^3 after the first 18 weeks of therapy. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of Leponex, haematological evaluation is required until haematological recovery has occurred.
If Leponex has been withdrawn and WBC count falls further to below 2000/mm^3 and/or the ANC falls below 1000/mm^3, the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated. It is recommended that the colony stimulating factor therapy be discontinued when the neutrophil count has returned to a level above 1000/mm^3.
Patients in whom Leponex has been discontinued as a result of white blood cell deficiencies (see above) must not be re-exposed to Leponex.
It is recommended that the haematological values be confirmed by performing two blood counts on two consecutive days; however, Leponex should be discontinued after the first blood count.

Table 1: Blood monitoring during the first 18 weeks of Leponex therapy

Blood cell count WBC/mm^3 (/L)	ANC/mm^3 (/L)	Action required
≥3500 (≥3.5 x 10^9)	≥2000 (≥2.0 x 10^9)	Continue Leponex treatment.
Between ≥3000 and <3500 (≥3.0 x 10^9 and <3.5 x 10^9)	Between ≥1500 and 2000 (≥1.5 x 10^9 and <2.0 x 10^9)	Continue Leponex treatment, sample blood twice weekly until counts stabilize or increase.
<3000 (<3.0 x 10^9)	<1500 (<1.5 x 10^9)	Immediately stop Leponex treatment, sample blood daily until hematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

Table 2: Blood monitoring after 18 weeks of Leponex therapy

Blood cell count WBC/mm^3 (/L)	ANC/mm^3 (/L)	Action required
≥3000 (≥3.0 x 10^9)	≥1500 (≥1.5 x 10^9)	Continue Leponex treatment.
Between ≥2500 and <3000 (≥2.5 x 10^9 and <3.0 x 10^9)	Between ≥1000 and <1500 (≥1.0 x 10^9 and <1.5 x 10^9)	Continue Leponex treatment, sample blood twice weekly until counts stabilize or increase.
<2500 (<2.5 x 10^9)	<1000 (<1.0 x 10^9)	Immediately stop Leponex treatment, sample blood daily until hematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

In the event of interruption of therapy for non-haematological reasons

Patients who have been on Leponex for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no hematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Leponex treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment (see section DOSAGE AND ADMINISTRATION).

Other precautions

Eosinophilia

In the event of **eosinophilia**, discontinuation of Leponex is recommended if the eosinophil count rises above 3000/mm^3. Therapy should be re-started only after the eosinophil count has fallen below 1000/mm^3.

Thrombocytopenia

In the event of **thrombocytopenia,** discontinuation of Leponex is recommended if the platelet count falls below 50,000/mm^3.

Cardiovascular disorders

In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see section DOSAGE AND ADMINISTRATION).

Orthostatic hypotension, with or without syncope, can occur during Leponex treatment. Rarely (about one case per 3000 Leponex-treated patients), collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing Leponex treatment require close medical supervision. Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of treatment and very rarely thereafter. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. If the diagnosis of myocarditis is confirmed, Leponex should be discontinued. Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, the treatment should be stopped unless the benefit clearly outweighs the risk to the patient.

Myocardial infarction

In addition, there have been postmarketing reports of myocardial infarction which may be fatal. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

QT interval prolongation

As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.
As with other antipsychotics, caution should be exercised when Leponex is prescribed with medicines known to increase the QTc interval.

Cerebrovascular adverse events

An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Leponex should be used with caution in patients with risk factors for stroke.

Risk of thromboembolism

Since Leponex may cause sedation and weight gain, thereby increasing the risk of **thromboembolism**, immobilization of patients should be avoided.

Metabolic Changes

Atypical antipsychotic drugs, including Leponex, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia

On rare occasions, severe hyperglycemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported during Leponex treatment in patients with no prior history of hyperglycemia. While a causal relationship to Leponex use has not been definitely established, glucose levels returned to normal in most patients after discontinuation of Leponex, and re-challenge produced a recurrence of hyperglycemia in a few cases. The effect of Leponex on glucose metabolism in patients with diabetes mellitus has not been studied. Impaired glucose tolerance, severe hyperglycemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycemia. 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. Exacerbation should be considered in patients receiving Leponex who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia or 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 antidiabetic treatment despite discontinuation of the suspect drug. In patients with significant treatment-emergent hyperglycemia, discontinuation of Leponex should be considered.
There is a risk of altering the metabolic balance resulting in slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including Leponex. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight Gain

Weight gain has been observed with atypical antipsychotic use, including Leponex. Clinical monitoring of weight is recommended.

Seizures

Leponex may lower seizure threshold. In patients with a history of seizures the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see section DOSAGE AND ADMINISTRATION).

Anticholinergic effects

Clozapine exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**. Probably on account of its anticholinergic properties, Leponex has been associated with varying degrees **of impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction**, **fecal impaction** and **paralytic ileus** (see section ADVERSE DRUG REACTIONS). On rare occasions these cases have proved fatal.

Fever

During Leponex therapy, patients may experience transient **temperature elevations** above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of **neuroleptic malignant syndrome** (NMS) must be considered. If the diagnosis of NMS is confirmed, Leponex should be discontinued immediately and appropriate medical measures should be administered.

Special populations

Hepatic impairment

Patients with stable pre-existing liver disorders may receive Leponex, but must undergo regular liver function tests. Such tests should be performed immediately in patients who develop symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia during Leponex treatment. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with Leponex must be discontinued. It may be resumed (see section DOSAGE AND ADMINISTRATION - Re-starting therapy) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Leponex.

Renal impairment

In patients suffering from mild to moderate renal impairment, an initial dose of 12.5 mg/day (half a 25 mg tablet) is recommended (see section DOSAGE AND ADMINISTRATION).

Patients aged 60 years and older

It is recommended that treatment be initiated at a particularly low dose (12.5 mg given once on the first day) and subsequent dose increments be restricted to 25 mg/day.
Clinical studies with Leponex did not include sufficient numbers of subjects aged 60 years and over to determine whether or not they respond differently from younger subjects.
Orthostatic hypotension can occur with Leponex treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking Leponex. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.
Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.

Patients aged 60 years and older with Dementia-related Psychosis

In patients aged 60 years and older with dementia-related psychosis, the efficacy and safety of clozapine has not been studied. Observational studies suggest that patients aged 60 years and older with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In the published literature, risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include sedation, the presence of cardiac conditions (e.g. cardiac arrhythmias) or pulmonary conditions (e.g. pneumonia, with or without aspiration). Leponex should be used with caution in patients aged 60 years and older with dementia.

Rebound, withdrawal effects

If abrupt discontinuation of Leponex 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 profuse sweating, headache, nausea, vomiting and diarrhoea.

Driving and using machines

Owing to the ability of Leponex to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

ADVERSE DRUG REACTIONS

Summary of the safety profile

The adverse effects of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (see section WARNINGS AND PRECAUTIONS).
The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever (see section WARNINGS AND PRECAUTIONS). The most common side effects are drowsiness/sedation, dizziness, tachycardia, constipation, and hypersalivation.
Data from the clinical trials experience showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leukopenia; somnolence; dizziness (excluding vertigo); and psychotic disorder.
Adverse drug reactions (ADRs) are listed by MedDRA system organ class (see Table 3). Within each system organ class, the adverse reactions are ranked by frequency, using the following convention: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 3: Treatment-Emergent Adverse Experience Frequency estimate from Spontaneous and Clinical Trial Reports

Blood and lymphatic system disorders	
Common	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon	Agranulocytosis
Rare	Anaemia
Very rare	Thrombocytopenia, thrombocythemia
Metabolism and nutrition disorders	
Common	Weight gain
Rare	Diabetes aggravated, impaired glucose tolerance, new onset diabetes
Very rare	Hyperosmolar coma, ketoacidosis, severe hyperglycemia, hypercholesterolemia, hypertriglyceridemia
Psychiatric disorders	
Common	Dysarthria
Uncommon	Dysphemia
Rare	Agitation, restlessness
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Seizures/convulsions/myoclonic jerks, extrapyramidal symptoms, akathisia, tremor, rigidity, headache,
Uncommon	Neuroleptic malignant syndrome
Rare	Confusion, delirium
Very rare	Tardive dyskinesia, obsessive compulsive symptoms
Eye disorders	
Common	Blurred vision
Cardiac disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, arrhythmias, myocarditis, pericarditis
Very rare	Cardiomyopathy
Vascular system disorders	
Common	Syncope, postural hypotension, hypertension
Rare	Thromboembolism
Respiratory disorders	
Rare	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal
Very rare	Respiratory depression/arrest
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, dry mouth
Rare	Dysphagia
Very rare	Intestinal obstruction/ileus/faecal impaction, parotid gland enlargement
Hepatobiliary disorders	
Common	Elevated liver enzymes
Rare	Pancreatitis, hepatitis, cholestatic jaundice
Very rare	Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Renal and urinary disorders	
Common	Urinary retention, urinary incontinence
Very rare	Interstitial nephritis
Reproductive system disorders	
Very rare	Priapism
General disorders	
Common	Benign hyperthermia, disturbances in sweating/temperature regulation, fatigue
Very rare	Sudden unexplained death
Investigations	
Rare	Increased CPK

Adverse drug reactions from spontaneous reports and literature (frequency not known)

The following adverse drug reactions (ADRs) were derived from post-marketing experience with Leponex via spontaneous case reports and literature cases and have been categorized according to MedDRA system organ class (see Table 4). Because these reactions have been reported voluntarily from a population of uncertain size and are subject to confounding factors, these post-marketing ADRs have been categorized with a frequency of "not known" since it is not possible to reliably estimate their frequency. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 4 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Nervous system disorders
Cholinergic syndrome, EEG changes
Cardiac disorders
Myocardial infarction which may be fatal, chest pain/angina pectoris
Respiratory disorders
Nasal congestion
Gastrointestinal disorders
Diarrhea, Abdominal discomfort/heartburn/dyspepsia
Hepatobiliary disorders
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
Musculoskeletal and connective tissue disorders
Muscle weakness, muscle spasms, muscle pain
Renal and urinary disorders
Renal failure, nocturnal enuresis

Very rare events of ventricular tachycardia, cardiac arrest and QT prolongation which may be associated with Torsades De Pointes have been observed although there is no conclusive causal relationship to the use of this medicine.

INTERACTIONS

Pharmacodynamic-related interactions

Anticipated pharmacodynamic interactions resulting in concomitant use not being recommended

Medicinal products known to have a substantial potential to depress bone marrow function should not be used concurrently with Leponex (see section WARNINGS AND PRECAUTIONS).
As with other antipsychotics, caution should be exercised when Leponex is prescribed with medicines known to increase the QTc interval, or causing electrolyte imbalance.

Observed pharmacodynamic interactions to be considered

Particular caution is recommended when Leponex therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other psychotropic agent, 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.
Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).
Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where Leponex 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.

Anticipated pharmacodynamic interactions to be considered

Clozapine may enhance the central effects of alcohol, MAO inhibitors and CNS depressants such as narcotics, antihistamines, and benzodiazepines.
Because of the possibility of additive effects, caution is essential when substances possessing anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly.
Owing to its anti-alpha-adrenergic properties, clozapine may reduce the blood pressure-increasing effect of norepinephrine or other predominantly alpha-adrenergic agents and reverse the pressor effect of epinephrine.

Pharmacokinetic-related interactions

Clozapine is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution is called for in patients receiving concomitant treatment with other substances that are either inhibitors or inducers of these enzymes.
No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines or type 1_c anti-arrhythmics, which are known to bind to cytochrome P450 2D6.

Observed pharmacokinetic interactions to be considered

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.
- Substances known to induce the activity of 3A4 and with reported interactions with clozapine include, for instance, carbamazepine, phenytoin and rifampicin.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.
- Substances known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4), fluvoxamine (1A2) and ciprofloxacin (1A2).
- 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 substances in combination with selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine (1A2), sertraline, fluoxetine or citalopram.

Anticipated pharmacokinetic interactions to be considered

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.
- Known inducers of 1A2 include, for instance, omeprazole and tobacco smoke. In cases of sudden cessation of tobacco smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.
- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations; no interactions have been reported to date, however.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING, AND FERTILITY

Women of child-bearing potential and contraceptive measures

Some female patients treated with antipsychotics other than Leponex may become amenorrheic. A return to normal menstruation may occur as a result of switching from other antipsychotics to Leponex. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Pregnancy

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

Non-teratogenic effects

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.
Antipsychotic drugs, including Leponex, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the suckling offspring. Therefore, mothers receiving Leponex should not breast-feed.

OVERDOSAGE

In cases of acute intentional or accidental Leponex 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 above 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 Leponex, 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 mg to 200 mg resulted in strong sedation or coma without being lethal.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyper-reflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnea, respiratory depression or failure.

Treatment

There are no specific antidotes for Leponex.
Gastric lavage and/or the administration of activated charcoal within the first 6 hours after Leponex ingestion. (Peritoneal dialysis and hemodialysis 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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Leponex has been shown to be an antipsychotic agent that is different from classic antipsychotics.
In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behavior. 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-alpha-adrenergic, anticholinergic, antihistaminic, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Pharmacodynamics (PD)

Clinically Leponex produces rapid and marked sedation, and exerts antipsychotic effects in patients with schizophrenia resistant to other antipsychotic agents. In such cases, Leponex has proven effective in relieving both positive and negative schizophrenic symptoms in short- and long-term trials.
Leponex is unique in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia. Furthermore, parkinsonian-like side effects and akathisia are rare. In contrast to classical antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynecomastia, amenorrhea, galactorrhea, and impotence.
Potentially serious adverse reactions caused by Leponex therapy are granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7% respectively (see section WARNINGS AND PRECAUTIONS).

Pharmacokinetics (PK)

Absorption

The absorption of orally administered clozapine is 90% to 95%; neither the rate nor the extent of absorption is influenced by food.
Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50% to 60%.

Distribution

In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 L/kg. Clozapine is approximately 95% bound to plasma proteins.

Biotransformation/metabolism

Clozapine is almost completely metabolized before excretion. Of the main metabolites only the desmethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration.

Elimination

Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days.
Only trace amounts of unchanged drug are detected in the urine and feces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the feces.

Linearity/non-linearity

Dosage increases from 37.5 mg to 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.

CLINICAL STUDIES

Clinical studies in treatment-resistant schizophrenia (Clozapine study 16 & 30)

The first study was Study 16, a randomized, double-blind, multicenter, parallel group comparative trial of clozapine versus chlorpromazine (CPZ) in hospitalized patients (aged 18 to 65 years and of either sex) with treatment resistant schizophrenia (DSM-II criteria). 151 such patients were randomly assigned to either clozapine (150-900 mg) or chlorpromazine (300-1800 mg) for 28 days with an optional extension up to 28 days (75 in clozapine group and 76 in chlorpromazine group). Efficacy was assessed by measuring mean change from baseline in the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) scores and the Nurses Observation Scale for Inpatient Evaluation (NOSIE-30). Throughout the study, and at endpoint, clozapine patients had a more rapid onset of action and showed significant improvement in BPRS items compared to chlorpromazine patients. At week 1, clozapine was statistically superior to CPZ in two items assessed: Motor retardation [0.67 vs. 0.12; p<0.05] and blunted affect [0.93 vs. 0.34; p<0.01]. At week 2, two more items also showed statistically significant improvements in clozapine group, emotional withdrawal [1.48 vs. 0.98; p<0.01] and unusual thought content [2.06 vs. 1.45; p<0.05]. At week 3, clozapine was statistically superior in 7 out of the 18 BPRS items assessed. At endpoint, clozapine showed statistically significant improvements in every item assessed. Results were similar for BPRS factors and CGI scores also. By week 2, statistically significant differences favoring clozapine were observed in the BPRS Total Score and maintained throughout the duration of study. Tests of comparative efficacy at endpoint showed clozapine to be significantly better for all five factors assessed: anxiety/depression (0.85 vs. 0.54; p<0.05), anergia (1.15 vs. 0.72; p<0.001), thought disturbance (1.80 vs. 1.28; p <0.01), activation (1.34 vs. 0.89; p<0.01), and hostile/suspiciousness (1.26 vs. 0.74; p<0.01)). At endpoint, clozapine showed statistically significant improvements in mean change in total BPRS score [22.53 vs. 14.64, p<0.001] and CGI [1.95 vs. 1.33, p<0.01]. Clozapine patients generally did better in the all NOSIE factors, except for social competence. Mean change from baseline showed statistically significant differences favoring clozapine in the improvement of irritability at weeks 3 (6.28 vs. 0.67, p<0.01) and week 4 (6.84 vs. 1.36, p<0.05). For most of the factors, particularly, total patient assets, there was clear evidence of an early onset of therapeutic benefit with clozapine, thus corroborating BPRS data, although no statistical difference was observed. At endpoint, clozapine was superior to CPZ for the following NOSIE factors: social interest (4.14 vs. 3.24), personal neatness (3.19 vs. 2.26), irritability (3.04 vs. 0.60) and manifest psychosis (6.32 vs. 4.24) as well as total assets (20.54 vs. 16.66).
Second study was Study 30, a randomized, double-blind, multicenter, parallel group, 6-week, comparative study of clozapine versus chlorpromazine plus benztropine. The study population included 319 treatment-resistant schizophrenic patients, between the ages of 18-60 years, who met DSM-III criteria for schizophrenia, refractory to treatment. Eligible patients were randomly assigned to either clozapine (up to 900 mg/day) or chlorpromazine plus benztropine (up to 1800 mg/day of chlorpromazine, plus 6 mg/day of benztropine). Efficacy was assessed using the BPRS score, CGI scale, and NOSIE-30. At the end of 6 weeks, clozapine was significantly superior to chlorpromazine in all "Positive", "Negative" and general symptoms of BPRS (p<0.001) except 'Grandiosity' and 'BPRS total score'. Clozapine showed a significantly superior change in CGI scale compared to chlorpromazine starting at week 1 (p<0.001). Clozapine was superior to chlorpromazine on all six NOSIE-30 factors and total assets starting at either week 1 or 2 (p < 0.05 to 0.001). Clozapine was statistically significant in the following NOSIE factors, social competence, social interest and personal neatness, and total assets (p<0.001), as well as irritability and motor retardation (p<0.01 <0.05, respectively).

Clinical study in risk of recurrent suicidal behavior (InterSePT Trial)

The effectiveness of clozapine in reducing the risk of recurrent suicidal behavior was assessed in the International Suicide Prevention Trial (InterSePT), a prospective, randomized, open label, international, parallel-group comparison of clozapine vs. olanzapine in patients with schizophrenia or schizoaffective disorder (DSM-IV) judged to be at risk for re-experiencing suicidal behavior, lasting for 24 months. A total of 956 patients were randomized to either clozapine (starting with 25 mg/day, titrated upwards to 200-900 mg/day) or olanzapine (5-20 mg/day). The primary efficacy measure was time to (1) a significant suicide attempt, including a completed suicide, (2) hospitalization due to imminent suicide risk (including increased level of surveillance for suicidality for patients already hospitalized), or (3) worsening of suicidality severity as demonstrated by "much worsening" or "very much worsening" from baseline in the CGI-SS-BP scale. Clozapine showed a statistically significant overall treatment effect compared to olanzapine for the primary efficacy measure (p=0.0309). Treatment effect for Type 1 events (a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance) was statistically significant in favor of clozapine (p=0.0316), with a hazard ratio [risk ratio] of 0.76 (95% C.I.: 0.58, 0.98). Similarly, the treatment effect for Type 2 events (worsening of suicidality severity as demonstrated by 7-point CGI-SS-BP change scale score of 6 or 7, or by implicit worsening of suicidality severity as demonstrated by occurrence of a Type 1 event) was statistically significant in favor of clozapine (p=0.0388), with a hazard ratio of 0.78 (95% C.I.: 0.61, 0.99). Probability (Standard Error, SE) of experiencing a Type 1 and Type 2 events was higher for olanzapine patients compared to clozapine patients at all visits. At week 104, the clozapine treatment group demonstrated a significantly lower probability of both Type 1 (24% vs. 32%; 95% C.I. 2%, 14%) and Type 2 event (28% vs. 37%; 95% C.I.: 2%, 15%).

NON-CLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential (for reproductive toxicity, see section WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREASTFEEDING, AND FERTILITY).

Mutagenicity

Clozapine and/or its metabolites were devoid of genotoxic potential when investigated for induction of gene mutations, chromosome aberrations and primary DNA-damage in a spectrum of *in vitro* mutagenicity tests. Likewise, no genotoxic activity was observed *in vivo* (bone marrow micronucleus test in mice).

Carcinogenicity

In Sprague-Dawley (CD) rats treated in the diet for 2 years, maximum tolerated doses of 35 mg/kg per day revealed no carcinogenic potential of clozapine. Likewise, no evidence of tumorigenic effects was obtained in two 1.5-year feeding studies in Charles River (CD) mice. In the first study, oral dose levels of up to 64 mg/kg per day were administered to males, and of up to 75 mg/kg per day to females respectively. In the second study, the highest dose for both sexes was 61 mg/kg per day.

Reproductive toxicity

No embryotoxic or teratogenic potential of clozapine was observed in rats or rabbits at daily oral doses of up to 40 mg/kg. In male rats receiving the same dosages for 70 days prior to mating, fertility was unaffected.
In female rats, fertility as well as pre- and postnatal development of the offspring was not adversely affected by oral clozapine treatment prior to mating (up to 40 mg/kg per day). When rats were treated at the same dosages during the later part of pregnancy and during lactation, survival rates of the young from lactating dams were lowered and the young were hyperactive. However, there was no lasting effect on pup development after weaning.

INCOMPATIBILITIES

Not applicable.

STORAGE

Do not store above 30 °C.
Leponex should not be used after the date marked "EXP" on the pack.
Leponex must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Any unused product or waste material should be disposed of in accordance with local requirements.

Manufacturer:
See folding box.

International Package Leaflet
Information issued: February 2013

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Novartis Pharma AG, Basel, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists