1. NAME OF THE MEDICINAL PRODUCT

Leponex® 25 mg tablets

Leponex® 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance*:* clozapine
Excipient with known effect: lactose*.*
For the full list of excipients, see section 6.1.

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 behaviour (see "Indications"),
- who have initially absolute neutrophil counts (ANC) ≥ 2,000 per mm^3, and at least 1,500 per mm^3 patients with documented Benign Ethnic Neutropenia (BEN).
- 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 "Warnings and precautions").

Myocarditis

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely.

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction.

If myocarditis or cardiomyopathy are suspected, Leponex treatment should be promptly stopped and the patient immediately referred to a cardiologist.

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

Increase mortality in elderly patients with dementia related psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times than seen in placebo-treated patients. Over the course of a typical 10 week-controlled trial, the rate of death in drug treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Leponex (clozapine) is not approved for the treatment of patients with dementia-related psychosis.

3. PHARMACEUTICAL FORM

25 mg and 100 mg tablets, divisible.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of resistant schizophrenic patients who are non-responsive to, or intolerant of classic neuroleptics.

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 risk for death.

4.2 Posology and method of administration

Posology/Administration

The dosage must be adjusted individually. For each patient, the lowest effective dose should be used. Cautious titration and a divided dosage regimen are necessary to minimise the risk of hypotension, seizures and sedation. The total daily amount may be divided into unequal doses, the largest of which should be taken at bedtime.

Prior to initiating treatment with clozapine tablets, a baseline ANC must be at least 2,000 per mm^3 for the general population; and must be at least 1,500 per mm^3 for patients with documented Benign Ethnic Neutropenia (BEN).

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacokinetic interactions with Leponex, such as benzodiazepines, carbamazepine or selective serotonin re-uptake inhibitors (see “Interactions”).

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 “Warnings and precautions”). Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately.

Method of Administration

Leponex is administered orally.

<u>Prerequisite actions and tests before starting treatment</u>

1. Medical examination, including a comprehensive psychiatric evaluation.
    - If the patient is a minor, the psychiatric evaluation must be performed by a pediatric psychiatrist. Additionally, the primary physician (pediatrician, family physician, community internist) must also perform a comprehensive examination.
2. Requisite baseline tests
    - Electrocardiogram (ECG) – including QTc interval.
    - Metabolic indicators – weight, BMI, blood pressure, level of fats in blood, level of lipids, fasting blood glucose, HbBA1C, complete blood count, including a differential

blood count and platelets.
- Kidney function and liver function.

3. The requisite baseline tests must be performed within a maximum of 10 days prior to the initial dispensing of the medicine.
4. The treating psychiatrist must explain the proposed integrated therapy program to the patient and instruct the patient to report any febrile illness or throat inflammation to the treating physician, since it will then become necessary to verify with an updated complete blood count (hereinafter: CBC) that there has been no drop in white blood cells.
5. It is recommended that, upon the initial treatment attempt with clozapine, all other antipsychotic medicines that the patient is taking should be gradually discontinued (clozapine monotherapy).

Course of treatment

A repeat prescription for clozapine may be issued by a treating psychiatrist or by a primary physician (family physician or pediatrician, community internist), provided that psychiatric monitoring is concurrently maintained.

The clinical situation should be monitored monthly by a psychiatrist until the optimal dosage is reached.

Requisite supervision and the dispensing of prescriptions

1. Leponex will be provided in community pharmacies or hospitals.
2. The first prescription (initiation of treatment) shall be dispensed only if the prescription was issued by a psychiatrist, and within a maximum of 10 days after the performance of the blood count.
3. The medicinal product shall be dispensed only according to a prescription that also specifies, in addition to the regular details, the following details (structurally, manually or as physically or digitally stamped):
   a. Confirmation that the blood count is normal, including the date of performance;
   b. Start date of the treatment with clozapine;
   c. Name of the examining physician.
4. During the first 18 weeks of treatment, the medicinal product shall be dispensed solely for one week of treatment.

   As of week 19 of the treatment, the medicinal product shall be dispensed solely for one month of treatment.
5. If treatment with clozapine is initiated during hospitalization – supervision and administration of the medicinal product will be performed by the hospital ward and, upon the patient's discharge, the supervision must be continued in the community. It is important to inform primary physicians about the treatment with clozapine and about the stage of supervision.
6. If treatment is initiated in the community (mental health clinic, psychiatric stabilizing facility, home hospitalization, etc.), the supervision and administration of the medicinal product will be performed in that framework. Inform primary physicians about the treatment and supervision.
7. During the first 18 weeks of treatment, the psychiatrist must perform weekly monitoring of the CBC and issue the weekly prescriptions accordingly. If a psychiatrist is unavailable, the family physician or pediatrician or community internist may perform the monitoring of the CBC and issue the prescription, in coordination with and according to the instructions of the psychiatrist. The treating physician must be informed of the blood test results within 48 hours. The supervision and clinical monitoring of the efficacy and safety of the patient's treatment must be performed at least once a month by the psychiatrist.
8. Subsequent to the first 18 weeks of treatment, the monthly prescription must be issued by a psychiatrist, subject to the results of the CBC that was taken not more than seven days earlier. If a psychiatrist is unavailable, a family physician or pediatrician may issue

the prescription, in coordination with and according to the instructions of the psychiatrist. The supervision and clinical monitoring of the efficacy and safety of the patient's treatment must be performed at least once every 3 months by the psychiatrist.

Table 1: Summary table of requisite monitoring

Test	Basic	First 18 weeks		After 6 months	Follow up after 1 year
		After 1 month	After 3 months		
CBC	X	Every week, later-on every month		every month	every month
Glucose in fast	X		X	X	Once a year
HbA1C	X		X		Once a year
Lipids (cholesterol and triglycerides)	X			X	Once a year
Blood chemistry	X	X		X	Once a year
ECG including QTc interval	X	Every 2 months in the first 4 months			Once a year
Constipation monitoring	X	Every week		X	Once a year
BMI	X			X	Once a year
Blood pressure and pulse	X	X	X	X	Once a year

Travel abroad

1. Due to the need to constantly monitor anyone taking this medicine, the patient must consult with the treating physician before booking the trip, in order to properly prepare for this.
2. The length of the vacation should be restricted according to the dates of performance of the requisite tests.
3. If a patient needs to be absent from Israel for a prolonged period, the patient must organize a schedule of tests and prescriptions at his destination, while coordinating in advance with the treating physician in the destination country.

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 few 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.

A lower starting dose and slower dose increases are recommended for patients with a history of seizures or with cardiovascular, renal or hepatic disorders.

For children and adolescents, begin at a dosage of 12.5 mg and gradually increase the dosage at a pace of 25 mg every 3 to 5 days, depending upon tolerance.

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.

The usual daily dose in the population of children and adolescents is in the range 125 to 475 mg.

It is recommended to reach a suitable dosage within a number of weeks, usually 300 mg per 24 hours, and to remain at this dosage for a number of weeks until clinical improvement is reached (if it is not possible to measure the clozapine levels in the blood) and/or until the appearance of side effects:

- Male smokers: 400-500 mg per 24 hours.
- Male non-smokers: 300-400 mg per 24 hours.
- Female smokers: 300-400 mg per 24 hours.
- Female non-smokers: 200-300 mg per 24 hours.

Nicotine per se does not affect the level of clozapine in the blood. Therefore, if electronic cigarettes or nicotine substitutes are used, there is no need to adjust the dosage.
The timeframe until there is a therapeutic response may be prolonged in some patients. Wait 6 months under optimal treatment before assessing the response to the medicine, because patients who showed no clinical response during the first three months, sometimes showed a Delayed response, within a timeframe of 3-6 months.

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 (the reason for reaching this dose should be documented).

If the level exceeds the maximum level in the blood of 600 ng/ml, consider, according to the clinical situation, reducing the dosage and/or adding an anticonvulsant medicinal product.

Factors that could alter the medicine level in the blood:

- A febrile illness raises the level of the medicine and could cause poisoning.
- Smoking lowers the level of the medicine in the blood.
- A sudden stop in smoking could increase the level of the medicine in the blood.

A psychiatrist must monitor the clinical situation once a month until the optimal dosage is reached.

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 “Warnings and precautions”).

(e.g. increased sweating, headache, nausea, vomiting and diarrhoea).

Re-starting 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 "Warnings and precautions"), but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution. Even for a patient who already proceeded to monthly CBCs after completing 18 weeks of weekly CBCs, increasing the dosage of the medicine once again requires at least 6 weeks of weekly CBCs after completing the increase in dosage. Subsequently, the monitoring can return to the frequency prior to the discontinuation. If clozapine was discontinued for more than one month, initiate monitoring as if restarting the treatment.

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.

Combination treatment with ECT

In acute cases of schizophrenia that are resistant to clozapine therapy, electroconvulsive therapy (ECT) may be added. A number of controlled studies and also a meta-analysis have shown benefit in adding ECT for some patients who did not respond adequately to clozapine alone. Before deciding to administer ECT, it is advisable to verify that the clozapine level in the blood is within the therapeutic range. In the event that ECT is added, reducing the clozapine dosage may be considered.

Reducing the risk of suicidal behaviour 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 “Warnings and precautions”).

Pediatrics

No pediatric studies have been performed. The safety and efficacy of Leponex in children and adolescents under the age of 16 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.

Measuring the clozapine level in the blood

1. Determining the medicine level in a patient’s blood enables the physician to ascertain whether the medicinal product is indeed within the effective therapeutic range, to avoid prescribing an unnecessarily high dosage, to examine treatment adherence and to detect resistant cases in which another increase in dosage is warranted. Determining the level is particularly important in instances when patients are taking a number of medicines, some of which might have a pharmacokinetic interaction with clozapine.
2. It is recommended to check the clozapine level in the blood 4-6 days after reaching the target dosage. It is advisable to take the sample about 12 hours after the latest dose is taken.
3. The recommended therapeutic level is within the range of 350 ng/ml and up to 600 ng/ml.
4. Factors affecting the medicine level in the blood:
   - Clozapine is metabolized in the liver (mainly cytochrome A21 and some A43) into two metabolites, with only one of them being active (norclozapine). The level of clozapine in the blood is influenced by medicinal products that affect these cytochromes (such as fluvoxamine, TCAs and cimetidine).
   - The level of the medicinal product in the blood is also influenced by gender (females metabolize less) and age (young people metabolize more), BMI, the genetics of metabolism, smoking, diet and more.
5. It is recommended to measure the level of clozapine in the blood throughout the treatment with clozapine in the following instances:
   - Inadequate clinical response to the treatment at a dosage of between 400 and 600 mg.
   - When unexpected side effects (such as a seizure) appear.
   - If a patient changed his/her smoking habits during the treatment.
   - After adding another medicine to the therapy that could affect the clozapine levels, such as fluvoxamine, TCAs (Tricyclic antidepressants), cimetidine.
   - Patients after bariatric surgery.
   - When the patient has pneumonia or other significant infection
   - In the appearance of symptoms suspicious of poisoning
6. Additional emphases about the need for measuring the level of the medicine in the blood:
   - When the clinical response at a dosage of up to 600 ng/ml is inadequate, the dosage may be gradually increased up to the level of 1,000 ng/ml, while monitoring the side effects.

4.3 Contraindications

- Known or suspected hypersensitivity to clozapine or any excipients listed in the composition of Leponex.
- Patients unable to undergo regular blood tests.
- History of granulocytopenia or agranulocytosis caused by drugs (with the exception of

granulocytopenia or agranulocytosis from previous chemotherapy).

- Impaired bone marrow function. Leponex treatment must not be given concomitantly with drugs that may suppress bone marrow.
- Uncontrolled epilepsy.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Multi morbidity of a patient with schizophrenia is not a contraindication.
- Circulatory collapse and/or central nervous system (CNS) depression of any cause.
- Severe renal or cardiac disorders, myocarditis.
- Acute liver disease associated with nausea, loss of appetite or jaundice; progressive liver disease; hepatic failure.
- Current and history of paralytic ileus.
- Leponex treatment must not be given concomitantly with drugs that can potentially cause agranulocytosis; concomitant use of depot antipsychotics is discouraged.

4.4 Warnings and precautions

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

Warnings
Potentially severe adverse effects of Leponex therapy are granulocytopenia and agranulocytosis, which occur with an estimated frequency of 3% and 0.7%, respectively. Agranulocytosis can be life-threatening.

Agranulocytosis
Agranulocytosis is defined as a drop in the number of neutrophils below 1,000 per mm^3. The cumulative incidence of agranulocytosis is about 1% and the reported mortality ratio (as a result of infection) ranges between 0.1% and 0.3%.

When the level of neutrophils is below 500 per mm^3, the immune-resistance becomes very low, resulting in an increased risk of a lethal infection (in the instance of Benign Ethnic Neutropenia – BEN, below 500 per mm^3). The prevalence of the effect varies depending upon the duration of the treatment. Most cases will appear during the first 18 weeks of treatment, but there have also been instances when the effect occurred later on.

In patients with no BEN diagnosis, if ANC count falls to between 1,000 and 1,500 per mm^3, haematological monitoring should be performed 3 times a week until value rises above 1,500 per mm^3. If ANC count falls between 500 and 999 per mm^3, clozapine is to be discontinued and haematological monitoring should be performed daily until value rises above 1,000 per mm^3. Once neutrophils rise back above 1,000 per mm^3, treatment with clozapine may be resumed, with monitoring 3 times a week until the level reaches 1,500 per mm^3. If ANC count falls below 500 mm^3, clozapine is to be discontinued immediately and haematological monitoring should be performed daily until value rises above 1,000 per mm^3. In any case, do not restart treatment (rechallenge) until neutrophils return to a value of at least 1,500 per mm^3 and consult with a hematologist. In patients with a BEN diagnosis, if ANC count falls to between 500 and 999 per mm^3, haematological monitoring should be performed 3 times a week until value rises above 1,000 per mm^3. If ANC count falls below 500 mm^3, clozapine is to be discontinued immediately and haematological monitoring should be performed daily until value rises above 500 per mm^3. In any case, do not restart treatment (rechallenge) until neutrophils return to a value of at least 1,000 per mm^3 and consult with a hematologist. For detailed summary, see table 2.

If the neutrophils fall below 1,500 per mm^3, or below 1,000 in case of a BEN diagnosis, strict monitoring must be performed as described below:

1. A prescription must not be issued to a patient until after the treating physician has verified that the results of blood count result are normal. Subsequent blood count data,

including the dates of the tests, must be centralized in a monitoring table in the patient's file. The prescription for the medicine shall record a quantity according to the dosage and the date of the check.

2. In any instance of any febrile illness (such as a throat inflammation, tonsil inflammation, systemic inflammation or the appearance of fever for any reason), a CBC must be performed immediately (explain this to patients before starting the treatment).
3. If thrombocytes fall below 50,000 per mm^3, discontinue the medicine and consult with a hematologist about the possibility of trying another therapeutic attempt.
4. If the number of neutrophils falls below the previous value by more than 50%, repeat the test within 4 days (see table 2 below).
5. Keep in mind that Benign Ethnic Neutropenia (BEN) exists among particular ethnic populations (such as among people of Yemenite or Ethiopian origin). In such instance, the baseline neutrophil count is low (typically lower than the norm by 500 – i.e., between 1,500 and 3,000). If BEN is suspected, consult with a hematologist and add the diagnosis to the patient's list of diagnoses. BEN is not a contraindication to treatment with clozapine.
6. If the number of leukocytes falls below the previous value by 50% (even if they don't reach a pathological level), consult with a hematologist. Keep in mind that a drop in the number of neutrophils is of the highest importance.

When neutrophils drop below 1,500 /mm^3, follow-up according to table 2. Table 2: Neutrophil monitoring scale:

Neutropenia severity	With BEN diagnosis	Level of neutrophils	Monitoring instructions	actions
no Neutropenia	no BEN	Higher than 1500 mm^3	Once a week for 18 weeks. Subsequently, once a month	
	BEN	Higher than 1000^3		
mild Neutropenia	no BEN	Between 1000 and 1499 per mm^3	Monitoring 3 times a week until value rises back above 1,500 per mm^3	After the value rises back above 1,500 per mm^3, resume normal monitoring frequency
	BEN		Normal level, no special monitoring is necessary	
Moderate Neutropenia	no BEN	Between 500 and 999 per mm^3	Daily monitoring until value rises back above 1,000 per mm^3	Discontinue treatment with clozapine. Once neutrophils rise back above 1,000 per mm^3, treatment with clozapine may be resumed, with monitoring 3 times a week until the level reaches 1,500 per mm^3. Subsequently, monitoring according to the duration of the treatment.
	BEN		Monitoring 3 times a week until value rises back above 1000 per mm^3	Continue treatment with clozapine. After neutrophils rise back above 1,000 per mm^3, resume normal monitoring frequency

Acute Neutropenia	no BEN	below 500 per mm^3	Daily monitoring until value rises back above 1,000 per mm^3	Immediately discontinue clozapine. In any case, do not restart treatment (rechallenge) until neutrophils return to a value of at least 1,500 per mm^3 and consult with a hematologist
	BEN		Daily monitoring until value rises back above 500 per mm^3	Immediately discontinue clozapine. In any case, do not restart treatment (rechallenge) until neutrophils return to a value of at least 1000 per mm^3 and consult with a hematologist

The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of white blood cell (WBC) and absolute neutrophil count (ANC) monitoring. The precautionary measures stated below are therefore mandatory.
Leponex must therefore only be used in schizophrenic patients in whom there is a demonstrated lack of response or inadequate response to other antipsychotic agents or who experience severe extrapyramidal side effects (in particular tardive dyskinesia) with other antipsychotic agents.
Leponex may also be used in schizophrenic and schizoaffective patients who are at long-term risk of recurrent suicidal behaviour, based on their clinical history or current clinical picture.

Patients with a history of drug-induced blood dyscrasia should on no account be treated with Leponex (see “Contraindications”).
Prescribing physicians must 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 or other symptoms such as fever or sore throat that indicate a possible infection. In such cases, a blood cell count must be performed immediately.

Special precautions
Haematology
In view of the risk of agranulocytosis, the following precautionary measures are mandatory:
Drugs known to have a substantial potential to suppress bone marrow function must not be used concomitantly with Leponex. Concomitant use of Leponex with depot antipsychotics must also be avoided because these potentially myelotoxic agents are only slowly eliminated from the body in emergency situations, e.g. in the event of granulocytopenia.
Patients with a history of primary bone marrow disorders should only be given Leponex if the benefit outweighs the risk. They should be examined by a haematologist prior to therapy.
The agreement of a haematologist must be obtained before giving Leponex to patients with a low white blood cell (WBC) count caused by benign ethnic neutropenia.

Other situations required Immediate discontinuation of Leponex treatment are:

Severe / life-threatening side effects and Patient who does not perform the routine blood tests.

If possible, the patient should be admitted to a specialist haematology unit, where protective isolation and administration of GM-CSF (granulocyte/macrophage colony-stimulating factor) or G-CSF (granulocyte colony-stimulating factor) may be indicated. It is recommended that

treatment with colony-stimulating factor be stopped once the ANC has again risen above 1.0 × 10^9/litre (1,000/mm^3).
In the event of infection, antibiotic therapy must be initiated immediately due to the risk of septic shock.
In patients in whom Leponex has been discontinued due to white blood cell deficiencies, Leponex treatment may be restarted (rechallenged) only as described in table 2 above, including consulting a haematologist where stated. It is recommended that the results of blood counts be confirmed by performing counts on two consecutive days. However, Leponex should be discontinued after the first blood count.
Leponex prescriptions must be marked “CBC” (= complete blood count) by the prescribing physician.
In the event of thrombocytopenia (see “Adverse effects”), Leponex should be discontinued if the platelet count falls below 50 × 10^9/litre (50,000/mm^3).

Other precautions

Cardiotoxicity

Before starting treatment with clozapine, run an ECG and verify that there are no conduction abnormalities.
Perform an ECG once every two months during the first four months of treatment; subsequently, once a year according to table 1. The length of the QTc interval must be documented in the patient’s file. The maximum QTc interval is 500 ms. In the event of prolongation, reduce the clozapine dosage and consult with a cardiologist. In the event of a gradual prolongation of QTc, it is recommended to perform ECG monitoring at a frequency of 3 times.
Patients with heart disease should be started on a low dose (1 x 12.5 mg on the first day). The dose increase should only be increased slowly and in small increments (see “Dosage/Administration”). Use in patients with severe cardiovascular disorders is contraindicated (see “Contraindications”). Patients with a history of heart disease or abnormal cardiac findings on physical examination should be referred to a specialist for further investigation, which should include an ECG Such patients should only receive Leponex if the expected benefits clearly outweigh the risks.
Orthostatic hypotension, with or without syncope, may occur during Leponex therapy. In rare cases (approx. one in 3,000 patients), collapse may be profound and may be accompanied by cardiac and/or respiratory arrest and possible fatal outcome. Such events are most likely during the initial titration phase in association with rapid dose escalation. In isolated cases, they have even occurred after the first dose. Such complications seem to occur more frequently with concomitant use of benzodiazepines or other psychotropic agents (see “Interactions”). Close medical supervision is therefore necessary at the start of Leponex therapy.
In patients diagnosed with cardiomyopathy while on Leponex treatment, there is the risk of developing mitral valve incompetence. Mitral valve incompetence has been reported in cases of cardiomyopathy related to Leponex treatment. These cases of mitral valve incompetence were mild or moderate in severity, detected on two-dimensional echocardiography (2D-Echo).
Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson’s disease.

Myocarditis and cardiomyopathy
In instances of a clinical suspicion of myocarditis (symptoms similar to flu, a drop in blood pressure, tachycardia, dyspnea, chest pain, ~~and~~ arrhythmias or symptoms of heart failure), perform an ECG and check the level of troponin, CRP, CBC and CK (creatine kinase). If myocarditis is suspected, immediately refer to an emergency room.
The symptoms may occur in rare cases during the first two months of treatment and very rarely thereafter (see “Adverse effects”). If these symptoms occur, particularly during the titration period, diagnostic measures should be initiated as quickly as possible to rule out myocarditis. The symptoms of clozapine-induced myocarditis may also resemble those of myocardial infarction or influenza. There have been reports of myocarditis in the post-

marketing period, including cases with a fatal outcome. The incidence of myocarditis as a result of clozapine is wide-ranging and ranges between 0.015-8.5%. There have also been reports of fatal cases of myocardial infarction. The assessment of causality was very difficult due to severe pre-existing cardiac disorders.
If myocarditis or cardiomyopathy is suspected, Leponex must be discontinued immediately and the patient referred to a cardiologist without delay.
The same signs and symptoms may also occur in the later stages of therapy and may then be associated with cardiomyopathy. In such cases, further investigation is indicated. If the diagnosis of cardiomyopathy is confirmed, Leponex must be discontinued. Patients who have had clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

Eosinophilia
Cases of eosinophilia (higher than 700 per mm^3) during treatment with clozapine (usually during the first month of treatment) have been associated with myocarditis (approximately 14%), pancreatitis, hepatitis, colitis, pericarditis/pericardial effusion or nephritis. This phenomenon can be part of a drug hypersensitivity syndrome (DRESS – Drug Reaction with Eosinophilia and Systemic Symptoms). Therefore, if eosinophilia appears, assess the systemic sensitivity symptoms (the appearance of a rash, allergic reactions, myocarditis or acute inflammatory reaction in any other organ) and, if there are, discontinue treatment with clozapine. Eosinophilia associated with clozapine, without inflammatory systemic effects, usually subside spontaneously, and therefore, the treatment may be continued while monitoring the ECG and performing weekly CBCs until the eosinophil count returns to normal. If the eosinophil count remains high for a number of weeks, even without systemic involvement, consult with a hematologist about further treatment or resume treatment with clozapine.

QT prolongation
As with other antipsychotic agents, caution is advised in patients with known cardiovascular disease or a family history of QT prolongation.
As with other antipsychotic agents, caution is advised when prescribing Leponex in conjunction with drugs known to increase the QTc interval.

Cerebrovascular events
An approximately 3-fold increase in the risk of cerebrovascular events has been seen in the dementia population with some atypical antipsychotic agents. The reason for this increased risk is not known. An increased risk cannot be ruled out for other antipsychotic agents or for other patient populations. Leponex should therefore be used with particular caution in patients with risk factors for stroke.

Seizures
Leponex may lower the seizure threshold.
The seizure ratio associated with clozapine is about 1% at a dosage of 150-300 mg per day and exceeds 3% at a dosage higher than 450 mg per day. At a dosage of higher than 600 mg per day (and when the level in the blood exceeds 600 ng/ml), the seizure ratio is higher. A correlation exists between the level of the medicine in the blood and the risk of seizures. A seizure episode is not an indication that clozapine should be discontinued. Consider adding an anticonvulsant medication. Alternatively, the clozapine dosage may be reduced. In any case, avoid administering carbamazepine.
For patients with a history of seizures, consider administering preventive anticonvulsant treatment before starting treatment with clozapine.
Patients with a history of epilepsy must be closely monitored during Leponex therapy since dose-related seizures have been reported (see “Interactions”). In such cases, the dose should be reduced. and If a patient has epilepsy, make sure that an anticonvulsant is used at a therapeutic level and consult with a neurologist if needed.
In the event of a clozapine-induced seizure, it is recommended to determine the clozapine level in the blood 12 hours after the latest dose, to suspend continuing the medicine by 24 hours and, if there are no further muscular contractions, reduce the next dose to half a dose.

If there are any doubts about continuation of the treatment or if there is a possibility that the seizures are not associated with clozapine, it is recommended to consult with a neurologist.
In patients with a history of seizures, treatment should be started with a single dose of 12.5 mg on the first day and the dose increase should be slow and in small increments (see "Dosage/Administration").

Fever
During Leponex therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence in the first three weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the white blood cell (WBC) count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. Neuroleptic malignant syndrome (NMS) must be considered as a possible cause in patients presenting with high fever. If NMS is diagnosed, Leponex treatment should be immediately stopped and the necessary therapeutic measures initiated.
At each consultation with the physician, the patient must be reminded of the importance of contacting the treating physician immediately at the first sign of fever, sore throat or other flu-like symptoms and especially of an infection which may be indicative of neutropenia. In such cases, a differential blood count must be performed immediately.

Risk of thromboembolism
Immobilisation must be avoided since Leponex may cause sedation and weight gain, thus increasing the risk of thromboembolism.

Falls
Leponex may cause seizures, somnolence, postural hypotension and motor and sensory instability that may lead to falls and resulting bone fractures or other injuries. An overall assessment of fall risk must be performed when initiating antipsychotic therapy in patients with illnesses, conditions or medications that may exacerbate these effects. This assessment should be repeated regularly in patients receiving long-term antipsychotic therapy.

Anticholinergic effects
Leponex possesses anticholinergic properties, which may lead to adverse effects throughout the body. Close monitoring is therefore required in the presence of prostatic enlargement and narrow-angle glaucoma. On account of its anticholinergic properties, Leponex may cause varying degrees of impairment to intestinal peristalsis, ranging from constipation to faecal impaction, intestinal obstruction, paralytic ileus, megacolon, bowel perforation and intestinal infarction/ischaemia. On rare occasions, these cases have been fatal (see "Adverse effects").

The reported incidence of constipation among clozapine patients is about 31% and of the development of ileus is 4%-8%.
The mortality rate among patients who develop paralytic ileus is 20%-25%. Therefore, ask the patient every week during the first 18 weeks and subsequently, every month, about constipation or a decrease in the frequency of bowel movements (and document responses in the patient's medical file). When necessary, an oral or osmotic laxative may be added or an enema may be used sporadically.
Particular caution is necessary in patients with a history of colonic disease or a history of lower abdominal surgery, receiving concomitant medications known to cause constipation (especially those with anticholinergic properties, e.g. various antipsychotic agents, antidepressants and antiparkinsonian agents), as these may exacerbate the situation. It is vital that constipation be recognised and actively treated.
Special precautions should be observed when considering co-administration with benzodiazepines (or other centrally-acting drugs; see "Interactions").

Metabolic changes
Atypical antipsychotic drugs, including Leponex, were associated with metabolic changes, which raise the cardiovascular/cerebrovascular risk. These metabolic changes may include

hyperglycaemia, dyslipidaemia and weight gain. While atypical antipsychotic drugs may cause some metabolic changes, each drug has its own specific risk profile within its drug class.
Treatment with clozapine leads to weight gain at a higher ratio than with all other antipsychotics and to a higher incidence of metabolic symptoms.

Hyperglycaemia.
Cases of diabetes mellitus, severe hyperglycaemia and even ketoacidosis or hyperosmolar coma have been reported, even in patients with no prior history of hyperglycaemia or diabetes mellitus. No causal relationship to Leponex has been established, although blood glucose levels returned to normal in most patients following discontinuation of Leponex. Re-exposure was positive in a small number of cases. The effect of Leponex on glucose metabolism in patients with pre-existing diabetes mellitus has not been studied. Patients with diabetes mellitus starting on antipsychotic drugs should have their blood sugar levels regularly monitored. Patients with risk factors of diabetes mellitus (e.g. excess weight, a family history of diabetes) starting on atypical antipsychotic drugs should have their fasting blood sugar levels tested prior to and regularly during treatment. The possibility of impaired glucose tolerance should be considered in patients treated with Leponex who develop hyperglycaemia with symptoms such as polydipsia, polyuria, polyphagia or weakness. Patients, who develop symptoms of hyperglycaemia during treatment with atypical antipsychotic drugs, should have their fasting blood sugar levels tested. In some cases, hyperglycaemia may return to normal after stopping treatment with atypical antipsychotic drugs. In other cases, hyperglycaemia may require further treatment despite stopping using atypical antipsychotic drugs. Discontinuation of Leponex should be considered in patients with significant treatment-related hyperglycaemia.

Diabetes
Diabetes may develop among clozapine patients at a higher incidence than among the general population.
Consequently, monitor the BMI, monitor metabolic indicators and monitor the fasting glucose levels and HbA1C (at a community mental health center or in documented coordination with the family physician) as specified in table 1.
In the event of significant changes in metabolic indicators, it is recommended to consider adding treatment for the metabolic side effect and, in extreme cases, to consider whether treatment with clozapine should continue, after consultation between the treating psychiatrist and the family physician, and while weighing benefit against risk.

Dyslipidaemia
Patients treated with atypical antipsychotic drugs, including Leponex, experienced undesired weight changes. Clinical monitoring, including baseline and regular follow-ups, is recommended.

Weight gain
Patients treated with atypical antipsychotic drugs, including Leponex, experienced weight gain. Clinical monitoring of weight is recommended.

Depression
If a patient develops major depression during treatment with clozapine, antidepressants having no interactions with other medicinal products may be used while taking clozapine (such as sertraline, citalopram, escitalopram or venlafaxine).

Special patient groups
Hepatic disorders
Patients with stable pre-existing liver disease may receive Leponex, but hepatic function must be regularly monitored. Liver function tests must be performed immediately in any patient developing symptoms of possible hepatic dysfunction (e.g. nausea, vomiting, loss of appetite) 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 only be resumed when the results of liver function tests return to normal. Close monitoring is necessary in such cases.

Renal disorders

Patients with mild to moderate renal impairment should be started on a low dose (1 x 12.5 mg on the first day) (see “Dosage/Administration”).

Elderly patients (≥60 years)

It is recommended that treatment be initiated at a lower dose in elderly patients (see “Dosage/Administration”).

Orthostatic hypotension may occur in patients treated with Leponex. There have been rare reports of tachycardia, which may be sustained. Elderly patients (≥60 years), particularly those with impaired cardiovascular function, may be more susceptible than others to these effects.

Some elderly patients may also be particularly susceptible to the anticholinergic effects of Leponex (e.g. urinary retention and constipation).

Psychosis/behavioural disorders in elderly patients with dementia

The risk of mortality was higher with atypical antipsychotic agents than with placebo in elderly patients (≥60 years) with dementia-related psychosis/behavioural disorders. Analysis of 17 placebo-controlled studies showed a mortality risk in this patient population that was 1.6 to 1.7 times higher than with placebo. Risk factors for higher mortality with antipsychotic agents are: sedation, cardiovascular disease (e.g. arrhythmias, sudden cardiac death) or pulmonary disease (e.g. pneumonia, with or without aspiration). Leponex is not approved for the treatment of psychosis/behavioural disorders in elderly patients (≥60 years) with dementia.

Rebound / withdrawal symptoms

If abrupt discontinuation of Leponex treatment is required (e.g. leukopenia), patients should be carefully monitored for recurrence of psychotic symptoms and symptoms associated with cholinergic rebound such as sweating, headache, nausea, vomiting and diarrhoea.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Clozapine is a substrate for many CYP450 isoenzymes, in particular 3A4, 1A2 and 2D6. This should minimise the risk of metabolic interactions caused by an effect on an individual isoform. Nonetheless, plasma clozapine levels should be closely monitored in patients receiving concomitant treatment with other drugs having an affinity for one or more of these enzymes.

Co-administration of substances that affect these isoenzymes may lead to a rise or fall in plasma levels of clozapine and/or the co-administered substances.

Theoretically, clozapine may cause an increase in plasma levels of tricyclic antidepressants, phenothiazines and type-1c antiarrhythmic agents known to bind to cytochrome P450 2D6. It may be necessary to prescribe lower doses. However, no clinically-relevant interactions have been reported so far.

The combination of Leponex with substances known to affect the activity of CYP450 isoenzymes may lead to a rise or fall in plasma levels of clozapine.

Inhibitors:

- The co-administration of enzyme inhibitors such as cimetidine (CYP1A2, 3A4 and 2D6 inhibitor) or erythromycin (CYP3A4 inhibitor), clarithromycin, azithromycin, fluvoxamine (1A2), perazine (1A2), ciprofloxacin (1A2) or oral contraceptives (1A2, 3A4, 2C19) with high doses of Leponex has been associated with elevated plasma clozapine levels and the occurrence of adverse effects.
- There have been reports of increased plasma clozapine levels in patients who received the drug in combination with fluvoxamine (CYP3A4 and CYP1A2 inhibitor; up to ten-fold increase) or other selective serotonin reuptake inhibitors (SSRIs) such as paroxetine (CYP1A2, 2D6 inhibitor), sertraline (CYP2C8/9, 2D6 inhibitor), fluoxetine (CYP2D6 inhibitor, up to two-fold increase) or citalopram (possibly a weak CYP1A2 inhibitor with what is probably the lowest potential of all SSRIs for clinically-significant interactions). However, there have been reports of clinically-relevant interactions following co-administration of citalopram and clozapine. Increased concentrations of clozapine have also been observed in patients who received the drug in combination with venlafaxine.
- Azole antimycotics and protease inhibitors are potent inhibitors/inducers of CYP3A4. They, too, may be expected to cause clinically-relevant interactions with clozapine. However, no interactions have been reported to date.

Substrates:
- Caffeine (substrate of CYP1A2) may raise plasma levels of clozapine. Plasma levels of clozapine fall by approx. 50% following a 5-day caffeine-free period. This should be kept in mind if there are changes in the consumption of tea or coffee. A significant increase in clozapine and N-desmethylclozapine was observed when concomitant treatment was given with 2 × 250 mg ciprofloxacin. There have also been reports of interactions with norfloxacin and enoxacin.

Inducers:
- Drugs that induce P450 CYP3A4 (e.g. carbamazepine and rifampicin) may reduce plasma clozapine levels. Withdrawal of concomitantly administered carbamazepine resulted in an increase in plasma clozapine levels.
- Concomitant use of phenytoin has been found to decrease plasma clozapine levels, resulting in reduced efficacy of a previously effective Leponex dose.
- Tobacco smoke induces CYP1A2. Sudden tobacco abstinence in heavy smokers may therefore lead to elevated plasma levels of clozapine and thus to increased adverse effects.
- Omeprazole is an inducer of CYP1A2 and CYP3A4 and an inhibitor of CYP2C19. There have been isolated reports of interactions with proton pump inhibitors (decreased concentrations of clozapine when given with omeprazole and pantoprazole or with combinations of lansoprazole and paroxetine).

Pharmacodynamic interactions
Drugs with substantial myelosuppressive potential should not be used concomitantly with Leponex. Long-acting depot antipsychotics (which have myelosuppressive potential) should not be used concomitantly with Leponex because these substances cannot be rapidly removed from the body if required, e.g. in the event of neutropenia (see “Special precautions” under “Warnings and precautions”).
Leponex may enhance the CNS effects of alcohol and MAO inhibitors as well as the CNS-depressant effects of narcotics, antihistamines and benzodiazepines. Fatalities have been reported for combinations of clozapine with such substances (including methadone).
Particular caution is advised when giving Leponex concomitantly with benzodiazepines or other psychotropic agents as well as in patients who were using such drugs until only a few days before initiation of Leponex therapy. In such cases, there is an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac or respiratory arrest. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment. It is advisable to avoid administering benzodiazepines. If necessary – preferably short-term.

Concomitant use of lithium or other CNS-acting drugs may increase the risk of neuroleptic malignant syndrome (NMS).
Due to the possibility of additive effects, particular caution is required when concomitantly administering drugs possessing anticholinergic, antihypertensive or respiratory-depressant properties. Owing to its anti-alpha-adrenergic properties, Leponex may reduce the pressor effect of noradrenaline or other predominantly alpha-adrenergic agents and may reverse the pressor effect of adrenaline. Leponex may lower the seizure threshold and adjustment of the antiepileptic dosage may therefore be necessary. There have been rare reports of severe epileptic seizures, including first occurrence of seizures and isolated cases of delirium when Leponex was co- administered with valproic acid. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Due to the risk of epileptic convulsions and hematologic disorders, avoid administering medicines that lower the seizure threshold, such as maprotiline or buproprion concomitantly with clozapine.
Leponex may increase plasma concentrations of highly protein-bound substances (e.g. warfarin and digoxin) due to their displacement from plasma proteins. If necessary, the dose of the protein-bound substance should be adjusted.
As with other antipsychotic agents, caution is advised when prescribing Leponex in conjunction with medicinal products known to increase the QTc interval or cause an electrolyte imbalance.
It is recommended to avoid administering medicines to lower blood pressure that are ACE inhibitors, antihistamines and barbiturates concomitantly with clozapine.

4.6 Fertility, pregnancy and breast-feeding

Pregnancy

No clinical data is available on use in pregnant women.
There have been no controlled studies in humans and the safety of Leponex in human pregnancy has therefore not been established. Particularly careful evaluation of the risk-benefit ratio of Leponex therapy is necessary in the event of pregnancy.
A return to normal menstruation may occur as a result of switching from other antipsychotic agents to Leponex. Appropriate contraceptive measures are therefore necessary in women of childbearing potential.

Neonates whose mothers have taken antipsychotic drugs in the third trimester are at risk of extrapyramidal motor symptoms and/or withdrawal symptoms following delivery. Restlessness, unusual hypertonia or hypotonia, tremor, somnolence, respiratory distress and nutrition disorders have been reported. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care and prolonged hospitalisation.
Antipsychotic drugs, including Leponex, should not be used in pregnancy unless clearly necessary. If discontinuation of treatment is required during pregnancy, it should not be done abruptly.

Breastfeeding

In animal studies, Leponex has been detected in the milk. Since it has an effect on infants, mothers undergoing treatment with Leponex should not breastfeed.

Fertility

Certain toxic effects have been observed in animal studies (see “Preclinical safety data”).

4.7 Effects on ability to drive and use machines

Leponex impairs the patient’s reactions and the ability to drive and to use tools or machines. Leponex has a sedative effect and may reduce the seizure threshold. Patients should therefore refrain from activities such as driving or using machinery, particularly during the first weeks of treatment.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions with clozapine are agranulocytosis, seizures, cardiovascular events and fever (see “Warnings and precautions”). The most common adverse effects are drowsiness/sedation, dizziness, tachycardia, constipation, nocturnal enuresis, hypersalivation (day and night) and sometimes also the appearance or exacerbation of obsessive symptoms.

The data from clinical studies showed that a varying number of patients treated with clozapine (7.1 to 15.6%) discontinued treatment due to adverse effects. The most common adverse effects leading to treatment discontinuation were leukopenia, somnolence, dizziness (excluding vertigo) and psychotic disorders.

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows*: “very common” (≥ 1/10); “common” (≥ 1/100 to < 1/10); “uncommon” (≥ 1/1,000 to < 1/100); “rare” (≥ 1/10,000 to < 1/1,000); “very rare” (< 1/10,000), “not known”* (frequency cannot be estimated from the available data).

Blood and lymphatic system disorders

Common: Leukopenia, decreased white blood cell (WBC), neutropenia.
Uncommon: Agranulocytosis.
Rare: Lymphopenia.
Very rare: Thrombocytopenia, thrombocytosis, anaemia.

There is a risk of granulocytopenia and/or agranulocytosis during Leponex therapy. Although generally reversible upon stopping treatment, agranulocytosis may result in sepsis and prove fatal.

The majority of cases of agranulocytosis (approx. 70%) occur during the first 18 weeks of therapy.

Prompt discontinuation of Leponex treatment is required to prevent the development of life-threatening agranulocytosis. Regular monitoring of the white blood cell (WBC) count is therefore mandatory (see “Special precautions”).

Unexplained leukocytosis and/or eosinophilia may occur, particularly during the first few weeks of Leponex treatment.

Metabolism and nutrition disorders

Common to very common: Weight gain (4 to 31%), which may be substantial.
Rare: Impaired glucose tolerance and diabetes mellitus, even in patients with no prior history of hyperglycaemia or diabetes mellitus.
Very rare: Severe hyperglycaemia, sometimes leading to ketoacidosis or hyperosmolar coma, even in patients with no prior history of hyperglycaemia or diabetes mellitus; hypertriglyceridaemia, hypercholesterolaemia.

Psychiatric disorders

Common: Dysarthria.
Uncommon: Stuttering (dysphemia).
Rare: Restlessness, agitation.
Very rare: Obsessive-compulsive disorders.

Nervous system disorders

Very common: Drowsiness and sedation (39 to 46%), dizziness (19 to 27%, with or without light-headedness).
Common: Headache, tremor, rigor, akathisia, extrapyramidal symptoms, seizures, convulsions, myoclonic jerks.
Rare: Confusion, delirium.

Leponex may cause EEG changes, including 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 dose increase and in patients with pre-existing epilepsy. In such cases, the dose should be reduced and, if necessary,

anticonvulsant therapy initiated. Carbamazepine should be avoided because of its potential to suppress bone marrow function; in the case of other anticonvulsant drugs, the possibility of a pharmacokinetic interaction should be considered. Fatal convulsions have been reported. Extrapyramidal symptoms are milder and less frequent than those that occur with conventional antipsychotic agents. Acute dystonia has not been confirmed as an adverse effect of Leponex therapy.
Very rarely, tardive dyskinesia has been reported in Leponex-treated patients who had been treated with other antipsychotic agents; a causal connection therefore cannot be established. Patients in whom tardive dyskinesia developed with other antipsychotic agents have improved on Leponex.

There have been uncommon reports of neuroleptic malignant syndrome (NMS) in patients taking Leponex either alone or in combination with lithium or other centrally-acting agents. In such cases, the drug must be discontinued immediately and intensive care instituted. The main symptoms of NMS are: rigor, hyperthermia, mental changes and autonomic lability.

Eye disorders
Common: Blurred vision.

Cardiac disorders
Very common: Tachycardia (particularly in the first weeks of treatment with Leponex; 25%).
Very rare: Cardiac arrest.
ECG changes (ST segment depression, flattening and inversion of the T wave, conduction disturbances) may frequently occur. There have also been isolated reports of cases of arrhythmia, pericarditis (with or without pericardial effusion), cardiomyopathies and myocarditis (with or without eosinophilia), some of which proved fatal. The clinical symptoms may resemble those of myocardial infarction or influenza. The diagnosis of myocarditis should therefore be considered in patients on Leponex who develop resting tachycardia accompanied by arrhythmias, dyspnoea or symptoms of heart failure. The treatment should be discontinued if this diagnosis is confirmed.
There have been very rare reports of cardiomyopathy. Leponex must be discontinued if cardiomyopathy is diagnosed.

Vascular disorders
Common: Hypertension, orthostatic hypotension, syncope.
Rare: Thromboembolism, including fatal cases and cases occurring in combination with organ necrosis (e.g. intestine); circulatory collapse as a result of severe hypotension, especially in association with aggressive dose titration, with the potentially severe consequence of cardiac or respiratory arrest.
The prevalence and severity of hypotension are affected by the rate and extent of dose increases.

Respiratory, thoracic and mediastinal disorders
Rare: Aspiration of ingested food (as a result of dysphagia).
Very rare: Respiratory depression, respiratory arrest. Pneumonia and lower respiratory tract infections, which may be fatal, have been reported during treatment with Leponex.

Gastrointestinal disorders
Very common: Constipation (14 to 25%), hypersalivation (31 to 48%).
Common: Nausea, vomiting, loss of appetite, dry mouth.
Rare: Dysphagia.
Very rare: Enlargement of the parotid gland, intestinal obstruction, paralytic ileus, faecal impaction.

Hepatobiliary disorders
Common: Elevated liver enzymes.
Rare: Hepatitis, jaundice, acute pancreatitis.
Very rare: Fulminant hepatic necrosis.

If jaundice develops, Leponex must be discontinued immediately (see “Other precautions” under “Warnings and precautions”).

Skin and subcutaneous tissue disorders
Very rare: Skin reactions.

Renal and urinary disorders
Common: Urinary incontinence, urinary retention.

Very rare: Tubulointerstitial nephritis, renal impairment, renal failure.

Reproductive system and breast disorders
Very rare: Priapism, impotence, changes in ejaculation, dysmenorrhoea.

General disorders and administration site conditions
Common: Fatigue, fever, benign hyperthermia, disturbances in sweating and temperature regulation.

Investigations
Rare: Elevated creatine phosphokinase (CPK).
Very rare: Hyponatraemia.
There have been very rare reports of ventricular tachycardia, cardiac arrest and QT prolongation, possibly associated with torsade de pointes, but there is no conclusive causal relationship to the use of this drug.

Fatalities during treatment
Unexpected sudden death is known to occur in psychiatric patients receiving conventional antipsychotic medication, but also in patients receiving no medication.
Such cases of sudden death have occurred with Leponex, even in younger patients. There may be a connection with the cardiovascular adverse effects of Leponex (ECG changes, arrhythmias, cardiomyopathies, myocarditis).

List of adverse drug reactions from post-marketing spontaneous reports (unknown frequency (cannot be estimated from the available data))

Infections and infestations
Sepsis.

Immune system disorders
Drug rash with eosinophilia and systemic symptoms (DRESS), angioedema, leukocytoclastic vasculitis.

Endocrine disorders
Pseudophaeochromocytoma.

Metabolism and nutrition disorders
Obesity.

Nervous system disorders
Cholinergic symptoms, EEG changes, pleurothotonus (Pisa syndrome), restless legs syndrome (RLS).

Cardiac disorders
Myocardial infarction (sometimes with fatal outcome), myocarditis (sometimes with fatal outcome) chest pain / angina pectoris, palpitations, atrial fibrillation, mitral valve incompetence associated with Leponex-related cardiomyopathy.

Vascular disorders
Hypotension.

Respiratory, thoracic and mediastinal disorders
Bronchoconstriction, pleural effusion, sleep apnoea syndrome, nasal congestion.

Gastrointestinal disorders

Megacolon and intestinal infarction/ischaemia (sometimes with fatal outcome), as well as intestinal necrosis, intestinal ulceration and bowel perforation with a possible fatal outcome, diarrhoea, abdominal discomfort, heartburn, dyspepsia, colitis.

Hepatobiliary disorders
Hepatic steatosis, hepatic necrosis, hepatotoxicity, liver fibrosis, liver cirrhosis, liver damage with associated life-threatening consequences such as liver failure, liver transplant and even death.

Skin and subcutaneous tissue disorders
Pigmentation disorder.

Musculoskeletal and connective tissue disorders
Rhabdomyolysis, muscle weakness, muscle spasms, muscle pain, systemic lupus erythematosus.

Renal and urinary disorders
Renal failure, nocturnal enuresis.

Reproductive system and breast disorders
Retrograde ejaculation.

General disorders and administration site conditions
Polyserositis.

Injury, poisoning and procedural complications
Falls (associated with Leponex-induced seizures, somnolence, postural hypertonia and motor and sensory instability).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose
Massive overdose, whether accidental or with suicidal intent, represents a serious danger to the patient.
In cases of acute intentional or accidental Leponex overdose for which information on the outcome is available, mortality to date is approx. 12%. Most of the fatalities were associated with heart failure or aspiration pneumonia and occurred at doses above 2,000 mg. There have been reports of patients recovering from an overdose in excess of 10,000 mg. However, in a few adults, 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 ingestion of 50 to 200 mg resulted in strong sedation or coma, without being lethal.

Signs and symptoms
Drowsiness, lethargy, coma, areflexia; confusion, hallucinations, agitation, delirium; extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, thermolability (possibility of extreme hypothermia); hypotension, collapse, tachycardia,

cardiac arrhythmia (in particular, AV block and extrasystoles), impaired cardiac conduction; aspiration pneumonia, dyspnoea, respiratory depression or respiratory failure.

Treatment

No specific antidote is known. The following non-specific measures are indicated:
Immediate and repeated gastric lavage followed by administration of activated charcoal within six hours of ingestion. Peritoneal dialysis and haemodialysis are unlikely to be effective.

Cardiorespiratory intensive care (ECG, continuous monitoring). Continuous monitoring of electrolyte and acid-base balance.
Peritoneal dialysis or haemodialysis in the event of oliguria or anuria (although this will not significantly increase the rate of elimination in view of the drug's high protein binding).

Some symptoms may respond to medical treatment, as follows:

- *Anticholinergic effects:* The parasympathomimetic agents physostigmine (crosses blood-brain barrier), pyridostigmine or neostigmine.
- *Arrhythmia:* Potassium, sodium bicarbonate or digitalis, depending on the symptoms; quinidine and procainamide are contraindicated.
- *Hypotension:* Infusion of albumin or plasma expanders. Dopamine and angiotensin are the most effective circulatory stimulants. Contraindicated: Adrenaline and other beta-sympathomimetics are contraindicated (may increase additional vasodilation).
- *Convulsions:* Diazepam i.v. or phenytoin slow i.v. long-acting barbiturates are contraindicated.

The patient should be monitored for at least 5 days because of the possibility of delayed reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N05AH02

Mechanism of action/Pharmacodynamics
Leponex, a tricyclic dibenzodiazepine derivative, is an antipsychotic agent that differs from conventional antipsychotic agents in terms of both its pharmacology and its clinical effect.
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 as well as potent anti-alpha-adrenergic, anticholinergic, antihistaminic and arousal-reaction-inhibiting effects. It also possesses antiserotoninergic properties.

Clinical efficacy
Clinically, Leponex produces rapid and marked sedation and exerts a potent antipsychotic effect, particularly in patients resistant to other drug treatment. In such cases, it brings about an improvement in both positive (productive) and negative symptoms of schizophrenia. A clinically significant improvement was observed in about one-third of patients within the first six weeks of treatment and in approx. 60% of patients in whom treatment was continued for up to 12 months. In addition, improvement has been described in some forms of perceptual dysfunction.
In a two-year study directly comparing Leponex with another atypical antipsychotic agent, it was shown that Leponex significantly reduced the risk of suicidal behaviour in patients with schizophrenia or schizoaffective disorder. There have been no studies on either of the acute effect of short-term treatment on suicidality or of the anti-suicidal effect in patients with other psychiatric disorders; use of Leponex in these indications is therefore not advisable. Leponex must not be used in patients who have depression with psychotic symptoms.
In the study, 980 patients were randomised to treatment either with Leponex or with the active control; 62% of the patients suffered from schizophrenia, 38% from schizoaffective disorder. For

statistical reasons, two types of suicidal events were evaluated (type 1 and type 2 events). After 2 years the cumulative probability of a type 1 event (i.e. unambiguous suicide attempt, completed suicide or hospitalisation to prevent suicide) was lower in patients treated with Leponex (24%) than in patients treated with the other atypical antipsychotic agent (32%):

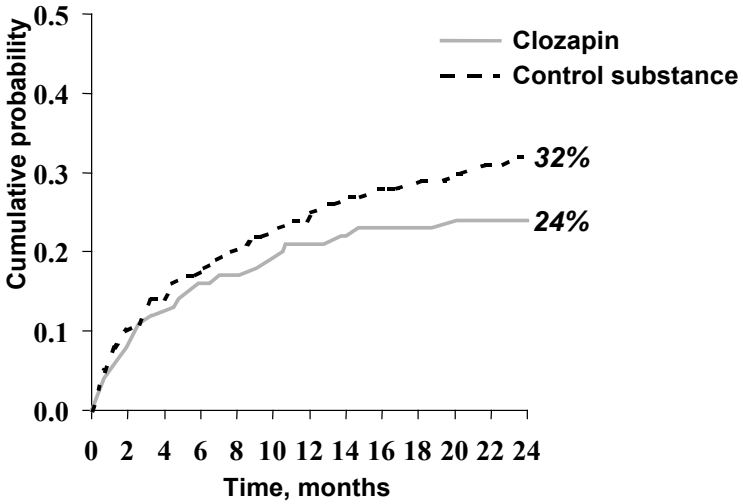

Figure*: Kaplan-Meier estimate of cumulative probability of an unambiguous suicide attempt, completed suicide or hospitalisation to prevent suicide (type 1 events).*

The rate of occurrence of type 2 events (suicidality other than type 1 events, assessed by several scores) was 28% with clozapine and 37% with the other atypical antipsychotic agent. Five successful suicides were reported in patients treated with clozapine and three in patients given the active control; this difference was not statistically significant.
Furthermore, epidemiological studies showed the rate of suicide and attempted suicide to be approximately seven times lower in Leponex-treated patients than in schizophrenic patients who did not receive Leponex.
Severe extrapyramidal reactions such as acute dystonia or full-blown parkinsonism are virtually unknown with Leponex, while Parkinson-like side effects and akathisia are rare. In contrast to conventional antipsychotic agents, Leponex causes little or no increase in prolactin levels, making adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea and impotence less likely.

5.2 Pharmacokinetic properties

Absorption
The absorption of orally administered Leponex is 90 to 95%; neither the rate nor the extent of absorption is influenced by food. The active substance of Leponex, clozapine, is subject to moderate first-pass metabolism; the absolute bioavailability is 50 to 60%. Peak blood levels are reached on average after 2.1 hours (range 0.4 to 4.2 hours) under steady-state conditions involving twice-daily administration.
Dose 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 trough plasma levels.

Distribution
The volume of distribution is 1.6 litres/kg. Clozapine is almost 95% bound to plasma proteins.

Metabolism
Prior to elimination, clozapine is almost completely metabolised by CYP1A2 and 3A4 and to some extent by CYP2C19 and 2D6.
Of the main metabolites, only desmethylclozapine is pharmacologically active. Its effect is

similar to that of clozapine but considerably weaker and of shorter duration.

Elimination

Elimination of clozapine is biphasic, with a mean terminal half-life of 12 hours (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 were detected in the urine and faeces. Approximately 50% of the dose administered is excreted as metabolites in the urine and 30% in the faeces.

Pharmacokinetics in special populations
Although no pharmacokinetic studies are available, the biotransformation and excretion data for Leponex indicate that particular caution is required in patients with hepatic, biliary or renal disease. Leponex is contraindicated in severe cases of such diseases due to the risk of accumulation.

5.3 Preclinical safety data
Mutagenicity
In vitro and *in vivo* tests provided no evidence that clozapine possesses any relevant mutagenic potential in humans.

Carcinogenicity
Following administration of maximum tolerated doses (35 mg/kg/day) in rats, clozapine did not show any carcinogenic potential. There was also no evidence of any tumorigenic effects in mice.

Reproductive toxicity
Studies on fertility and the early stages of embryonic development in rats showed effects on implantation and fetal growth starting at doses of 40 mg/kg. The exposure in rats was higher, by a factor of about 6, than the exposure in humans given a dose of 0.74 mg/kg. Abortions were reported in 5 rabbits given a dose of 20 mg/kg; post-natal effects were reported, but their significance for an assessment of human risk is not known.
Lactation/post-natal development: When female rats were given doses of up to 40 mg/kg during the later part of pregnancy and during lactation, survival rates of the offspring were lowered and the offspring were hyperactive. However, there was no lasting effect on the development of the offspring after weaning and the relevance of these observations for humans is not clear.

6. PHARMACEUTICAL PARTICULARS

6.1 list of excipients
Lactose monohydrate; maize starch; povidone; talc, silica colloidal anhydrous; magnesium stearate.

6.2 Incompatibiliti
es Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store above 25°C.
Keep out of the reach and sight of children.

6.5 Nature and contents of container
25 mg *tablets* (with score line, divisible): 50 tablets in a pack.
100 mg *tablets* (with score line, divisible): 50 tablets in a pack

7. REGISTRATION HOLDER

Devries&Co.
Ltd.
32 HaBarzel St.
Tel Aviv

8. MANUFACTURER

Mylan Pharma GmbH
Turmstrasse 24
6312
Steinhausen
Switzerland.

9. MARKETING AUTHORISATION NUMBERS

Leponex 25 mg tablets: 058-75-23147

Leponex 100 mg tablets: 047-98-23148

Revised in December 2023 according to MOH guidelines.