

**Patient leaflet in accordance with the Pharmacists' Regulations
(Preparations) - 1986**

This medicine is dispensed with a doctor's prescription only

Leponex 25 mg tablets

Leponex 100 mg tablets

Active ingredient:

Each tablet contains:
Clozapine 25 mg

Each tablet contains:
Clozapine 100 mg

Inactive ingredients and allergens: See section 6 under 'Additional information' and 'Important information about some of this medicine's ingredients' in section 2.

Preparation dispensing instructions:

During the first 18 weeks:

Perform a blood test once a week during the first 18 weeks.

The community pharmacy will dispense the medicine for one week of treatment only, according to a doctor's prescription, provided that it carries the stamp:

"White blood cell test was performed, and the results are normal".

Starting from week 19 of treatment:

A blood test must be performed at least once a month.

The community pharmacy will dispense the medicine for one month of treatment only, according to a doctor's prescription, provided that it carries the stamp:

"White blood cell test was performed, and the results are normal".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

Before starting treatment with Leponex, blood tests must be performed to make sure that you can take the medicine.

1. What is this medicine intended for?

Leponex is used for treatment in resistant schizophrenic patients who are non-responsive to, or intolerant of other antipsychotic medicines.

The medicine is also intended for reducing the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder who are long-term risk due to suicidal behaviour, based on previous history.

Therapeutic group: Atypical antipsychotics.

A schizoaffective disorder is a combination of schizophrenia with mood disorder.

Suicidal behaviour - actions by a patient that put him/her at risk of death.

2. Before using the medicine

Do not use this medicine if:

- you are sensitive (allergic) to the active ingredient or any of the other ingredients in this medicine (see section 6).
- you are unable to undergo regular blood tests.
- you suffer from severe liver or kidney disease.
- you suffer from heart disorders or inflammation of the heart muscle (myocarditis).
- you suffer from disorders such as uncontrolled epilepsy or alcoholic or other forms of intoxication.
- you are in a deep state of unconsciousness or blood flow failure (circulatory collapse).
- you are suffering or have suffered in the past from a bowel obstruction (paralytic ileus).
- you have a history of granulocytopenia or agranulocytosis caused by a drug (with the exception of granulocytopenia or agranulocytosis from previous chemotherapy).
- you take medicines that could cause agranulocytosis.
- you suffer from impaired bone marrow function. Do not take Leponex if you take medicines that may suppress bone marrow.
- you take antipsychotics with long-acting antipsychotics (depot).

Special warnings about using this medicine

Before using Leponex, tell your doctor if:

- you suffer from liver, kidney disease or heart disease.
- you suffer from an enlarged prostate gland, seizures, glaucoma, allergies or other disorders.
- you suffer from diabetes (high blood sugar level). Your doctor will need to check your blood glucose levels regularly.

When is caution required when taking Leponex?

- Extended periods of immobility, such as remaining in bed for an extended period of time, should be avoided to prevent problems with circulation (the formation of blood clots).
- Leponex may increase the likelihood of muscle cramps. If you suffer from epilepsy, the likelihood of experiencing a seizure may be increased by treatment with Leponex.

Why do regular blood count tests need to be performed?

Serious blood count changes (a lack of white blood cells) may occur during treatment with Leponex. This disorder can be cured by identifying it early on and stopping the medicine immediately (this must only be done under the direction of a doctor). It is therefore important for you to have regular blood count tests performed:

Once per week during the first 18 weeks after the start of treatment, then later on at least once per month.

Even after Leponex has been stopped altogether, your doctor will still perform blood count tests. Symptoms of this change in blood count include fever, chills, sore throat, tonsillitis, systemic inflammation and impaired wound healing. At the first sign of such problems, you must contact your doctor immediately. Your doctor will check your blood count right away and take other steps if necessary.

You should inform your doctor immediately if you experience the following states or symptoms during treatment with Leponex:

- High fever, muscle stiffness, rapid breathing, abnormal sweating or a loss of alertness (clouded consciousness). It is possible that your body might not be reacting properly to the medicine.
- Circulatory collapse (signs may include suddenly feeling weak, dizziness, cold sweats, vision problems and loss of consciousness), cardiac arrhythmias.
- Inflammation of the heart muscle or the sac around the heart (signs include palpitations, shortness of breath, agitation, rapid tiring, pain behind the breastbone, flu-like symptoms, fever, rapid breathing and swelling in the legs).
- Thromboembolism (acute blockage of blood vessels due to a displaced blood clot; signs include pain in one leg and/or swelling in one leg, sudden breathing problems, bluish discoloration).
- Inflammation of the liver (hepatitis, signs include nausea, vomiting or loss of appetite) or jaundice.
- Constipation.

The following side effects may occur during treatment with Leponex:

- When taking Leponex, light-headedness or fainting may occur due to a drop in blood pressure, especially at the start of treatment.
- Seizures, drowsiness, fainting, muscle weakness; these may result in falls.
- Chest pain, which may be a symptom of a heart attack that can result in death.
- Chest pain, which may be due to inflammation of the heart muscle and can result in death.
- Abdominal pain and constipation as possible signs of abnormal widening of the large intestine, which can result in death.
- Abdominal pain, which may be a sign that part of the intestine is dying off due to inadequate blood flow and can result in death.
- Leponex may cause drowsiness and more time in bed with weight gain, which may result in blood clots forming in some patients.

There have been cases of fatal heart attacks under Leponex. Because Leponex may cause drowsiness, the combination of increased time in bed and weight gain may cause blood clots.

For the complete list of side effects, see section 4, "Side effects".

Smoking

If you are a smoker or consume other forms of nicotine, increased concentrations of the active ingredient in Leponex may occur in your blood if you suddenly give up smoking or nicotine use. This may result in increased side

effects. **Inform your doctor** of any such change in your habits, as a dose adjustment may be required.

Children and adolescents

The safety and efficacy of Leponex in children below the age of 16 has not been proven.

Tests and follow-up

Prerequisite actions and tests before starting treatment

- Medical examination, including a comprehensive psychiatric evaluation.
- Electrocardiogram (ECG) test.
- Measurement of blood pressure and pulse.
- Metabolic indicators – weight, BMI, level of fats in blood, level of lipids, fasting blood glucose level, glycated hemoglobin (HbA1C), complete blood count, including a differential blood count and platelets.
- Kidney function and liver function.

Follow-up required during treatment

- ECG test.
- Measurement of blood pressure and pulse.
- If you suffer from diabetes (high blood sugar level), you will be asked to check your blood glucose level regularly.
- Leponex may cause changes in blood fats and result in weight gain. Your doctor may monitor your weight and blood fat levels.
- Regular blood tests must be performed throughout treatment and for 4 weeks after the end of treatment. Your doctor will instruct you when you need to take the tests.

Your doctor may perform additional tests. It is important to have all the blood tests performed as recommended by your doctor.

Travel abroad

- Due to the need to constantly monitor anyone taking this medicine, you must consult with your doctor before planning the trip, in order to properly prepare for this.
- The length of your vacation will likely be restricted according to the dates of performance of the required tests.
- If you need to be overseas for a more prolonged period, you will need to organize a schedule of tests and prescriptions at your destination, while coordinating in advance with the treating physician in the destination country.

Drug interactions

If you are taking or have recently taken other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:

- Sleep medications or tranquilizers such as benzodiazepines, barbiturates.
- Anti-allergy medicines.
Leponex strengthens the effects of these medicines.

Other medicines that may have an interaction with Leponex include:

- Medicines to treat epilepsy (phenytoin, valproic acid, carbamazepine).
- Medicines to treat depression (lithium, fluvoxamine, tricyclic antidepressants, MAO inhibitors, citalopram, paroxetine, fluoxetine, sertraline, bupropion, maprotiline, venlafaxine).
- Medicines to reduce high blood pressure.
- Medicines to treat HIV infections (AIDS).
- Medicines to treat peptic ulcers (cimetidine, omeprazole, pantoprazole, lansoprazole).
- Medicines to treat fungal infections (antifungal preparations) and antibiotics (erythromycin, clarithromycin, azithromycin, rifampicin, fluvoxamine, praziquantel, ciprofloxacin).
- Anti-diarrhoea medications.
- Caffeine.
- Birth control pills.
- Other medicines for the treatment of psychiatric disorders, including long-acting medicines (depot).
- Narcotics and other medicines that can affect your breathing.
- Medicines known to increase the QTc interval or cause an electrolyte imbalance.
- A medicine to prevent blood clots, warfarin.
- Anticholinergic medicines to relieve stomach cramps and spasms and travel sickness.
- A medicine for treatment of heart problems, digoxin.
- Adrenaline, to treat emergency situations.

Using this medicine and alcohol and caffeine consumption

During your treatment with Leponex, do not drink alcohol, as Leponex may strengthen the effect of alcohol.

Inform your doctor of a change in the number of caffeine-containing beverages you consume in a day.

Pregnancy, breastfeeding and fertility

Do not use this medicine without consulting your doctor before beginning treatment if you are pregnant, planning on becoming pregnant or breastfeeding.

Pregnancy

There is no information on the efficacy and safety of Leponex when used during pregnancy. During pregnancy, Leponex should only be taken if expressly prescribed by a doctor. Infants whose mothers had taken antipsychotic medicines during the third trimester are at risk for the following symptoms after birth: stiff limbs, tremor, agitation, stiff muscles, muscle weakness, drowsiness, shortness of breath and nutritional problems. In some cases, the symptoms are self-limiting, while in others the new-born infants require care in an intensive care unit and face prolonged hospitalisation.

Please tell your doctor immediately if you are or believe you may be pregnant so that they can discuss with you how to proceed. Under no circumstances should you stop the treatment on your own initiative. Suddenly stopping Leponex can have severe consequences. Please tell your gynaecologist or obstetrician immediately that you have been taking the medicine during pregnancy, especially if your child experiences the problems described above after they are born.

Breastfeeding

Because Leponex is excreted in human milk, mothers being treated with Leponex should not breastfeed.

Fertility

Some women taking certain antipsychotic medicines have no or irregular periods. Your periods may return when the treatment with another antipsychotic medicine is changed to treatment with Leponex. In these circumstances, you should use a reliable method of contraception.

Driving and using machines

Leponex may cause drowsiness, primarily at the start of treatment. Therefore, patients must refrain from activities such as driving or using machines, especially during the initial weeks of treatment.

Important information about some of this medicine's ingredients

The medicine contains lactose. If you have been told by the doctor that you have an intolerance to certain sugars, consult with the doctor before taking Leponex.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine.

The standard dose is generally:

The treatment begins with one half of a 25 mg tablet (12.5 mg) once or twice on the first day. Your doctor will gradually increase your dose, until the ideal dose for you is determined.

Your treatment will continue with a daily dose of Leponex between 300 and 450 mg. The daily dose is usually taken in divided portions, some taken in the

morning and some at bedtime. Some patients may require doses of up to a maximum of 900 mg per day.

Your doctor may change the required dose if you smoke, suffer from heart disease, kidney/liver problems, are 60 or older or take other medicines.

Do not exceed the recommended dose.

The dosage is adjusted by a doctor for the individual patient according to the severity of their disorder. To achieve a good treatment outcome, you must follow the dosage instructions from your doctor.

Therefore, do not change the prescribed dose on your own. If you feel that the medicine is too weak or too strong, talk to your doctor or pharmacist.

Take the medicine with a small amount of water.

Leponex 25 mg and 100 mg tablets have a score line and can be divided.

There is no information about crushing and chewing the tablet.

If you have accidentally taken a higher dose, refer to your doctor or pharmacist straight away. You may require medical attention.

If you have taken an overdose or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

Signs and symptoms of overdose:

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.

If you forget to take the medicine at the scheduled time, take a dose as soon as you remember, however, if it is time to take your next dose or less than 4 hours remain before your next dose, skip the forgotten dose, and take your next dose at the right time. Never take two doses together to make up for the missed dose.

If you have not taken Leponex for more than two days, do not resume taking the medicine and refer to your doctor as soon as possible.

Even if your health improves, do not stop taking this medicine without consulting your doctor.

If you stop taking this medicine

You should not interrupt treatment with Leponex without consulting your doctor as interrupting treatment may cause side effects. If you need to stop treatment with Leponex, your doctor will reduce the dose gradually over 1 to 2 weeks in order to avoid side effects. If it is necessary to stop the medicine suddenly, the following psychotic and withdrawal symptoms may occur: increased sweating, headache, nausea and diarrhoea, as well as bronchial constriction. **Inform your doctor immediately if you notice these symptoms as they should be treated immediately.**

Do not take medicines in the dark! Check the label and dose every time you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with all medicines, using Leponex may cause side effects in some users. Do not be alarmed by this list of side effects. You may not experience any of them.

The most common serious side effect of Leponex is a severe deficiency of white blood cells. Additional serious side effects are cardiovascular events and fever.

Very common side effects include drowsiness, dizziness, rapid heartbeat, constipation, increased or reduced salivation, night-time wetting.

Common side effects include weight gain, seizures, speech problems, headaches, spasms and muscle twitches or muscle stiffness, tremor, agitation (also known as extrapyramidal symptoms), akathisia (involuntary movements), unconsciousness, fainting, blurred vision, drop in blood pressure when switching from lying down/sitting to standing, high blood pressure, ECG changes, nausea, vomiting, lack of appetite, dry mouth, elevated liver enzymes, bladder dysfunction, tiredness, changes in sweat secretion and impaired temperature regulation.

Uncommon side effects include muscle cramps, disorientation and blood pressure fluctuations.

Rare side effects include impaired glucose tolerance and diabetes, elevated blood sugar levels (hyperglycaemia that may in rare cases lead to a build-up of acids in the blood (ketoacidosis) or a coma), restlessness, excitement, confusion, severe confusion (delirium), compulsive thoughts and behaviours, heart arrhythmias, inflammation or disease of the heart muscle or inflammation of the sac around the heart (signs include palpitations, shortness of breath, agitation, rapid tiring, pain behind the breast bone, flu-like symptoms, fever, rapid breathing or swelling in the legs), circulatory collapse, problems swallowing (may lead to food aspiration), difficulties breathing, respiratory infections, inflammation of the liver (hepatitis C), jaundice and inflammation of the pancreas, thromboembolism (acute blockage of blood vessels by a shifting blood clot, signs include leg pain on one side and or swelling in one leg, sudden breathing problems and bluish discolouration), severe drop in blood pressure, lymphopenia (decline in the number of lymphocytes in the blood), elevated level of the enzyme creatine phosphokinase.

Very rare side effects include enlargement of the parotid gland, intestinal obstruction (paralytic ileus), fecal impaction, skin reactions, high cholesterol and high blood lipid levels, cardiac arrest, kidney function problems and problems with sexual function (impotence, prolonged erection, changes in ejaculation), dysmenorrhoea, thrombocytopenia (drop in the number of platelets in the blood), thrombocytosis (a high number of platelets in the blood), anaemia, respiratory depression, respiratory arrest, pneumonia and lower respiratory tract infection, low blood sodium level (hyponatremia).

Side effects of unknown frequency (the frequency of these effects has not been established yet) include:

- Liver problems such as fatty liver, liver cell death and liver damage.

- Liver problems that replace normal liver tissue with scar tissue and thus result in a loss of function that may even lead to a life-threatening situation. This includes liver failure, liver damage and liver transplant.
- Sporadic 'pounding', 'hammering' or 'fluttering' feeling in the chest (rapid heartbeat).
- Falls due to seizures, drowsiness, fainting or muscle weakness triggered by Leponex.
- Chest pain, which may be a symptom of a heart attack that can result in death.
- Chest pain, which may be a sign of inflammation of the heart muscle and can result in death.
- Chest pain, hiccups and rapid breathing (signs of an accumulation of fluid between the layers of tissue covering the lungs and lining the chest cavity).
- Rapid and irregular heartbeat (atrial fibrillation), heart palpitations, fainting, shortness of breath or chest problems may occasionally occur.
- Abdominal pain with fever and/or constipation or bloody diarrhoea as possible signs of potentially life-threatening bowel disease, intestinal necrosis, intestinal ulceration, bowel perforation, diarrhoea, abdominal discomfort, heartburn, dyspepsia.
- Muscle spasms, fever and reddish-brown urine as a possible sign of abnormal breakdown of the muscles (rhabdomyolysis).
- Varying degrees of pain in the chest and abdomen as possible signs of simultaneous inflammation of membranes in multiple body cavities, for example the membranes in the chest, abdomen and joints.
- Proven or strongly suspected infection involving a fever or low body temperature, unusually rapid breathing, rapid heartbeat, changes in communicability and consciousness and a drop in blood pressure (sepsis).
- Pauses in breathing or phases of flat breathing during sleep.
- Allergic reaction (swelling primarily in the face, mouth and tongue that may be accompanied by itching or pain).
- Extensive skin rash with fever.
- Night-time wetting.
- Rash, purple/red spots, fever or itching due to inflammation of the blood vessels.
- Inflammation of the colon resulting in diarrhoea, abdominal pain and fever.
- Change in skin colouration.
- 'Butterfly rash' in the face, joint pain, muscle pain, fever and tiredness (lupus erythematosus), muscle weakness.
- Inflammation of the tissues lining the internal organs (serositis).
- Sudden, uncontrollable rise in blood pressure (pseudophaeochromocytoma).
- Low blood pressure.
- Uncontrolled bending of the body to one side (Pisa syndrome).
- Excessive weight gain (body mass at least 20% higher than it should be).
- An irresistible urge to move the legs (Restless legs syndrome, RLS) accompanied by an unpleasant feeling in the legs.
- Neuroleptic malignant syndrome.
- Nasal congestion.
- Kidney failure.
- In men: an ejaculation problem involving semen entering the bladder instead of being ejaculated through the penis (dry orgasm or retrograde ejaculation).
- See a urologist immediately if you experience a prolonged, painful erection without sexual stimulation (known as priapism).

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link "Reporting Side Effects of Drug Treatment" on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: <https://sideeffects.health.gov.il>

5. **How to store the medicine?**

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package and tray. The expiry date refers to the last day of that month.

Storage conditions

- Do not store above 30°C.

6. **Additional information**

In addition to the active ingredient, this medicine also contains:

Lactose monohydrate; maize starch; povidone; talc; colloidal anhydrous silica; magnesium stearate.

What the medicine looks like and contents of the pack:

Leponex 25 mg is dispensed as a circular, flat, yellow, bevelled edged tablet, coded "SANDOZ" on one side, "L/O" and score line on the other side.

Leponex 100 mg is dispensed as a circular, flat, yellow, bevelled edged tablet, coded "SANDOZ" on one side, "Z/A" and score line on the other side.

Both doses are marketed in packages of 50 tablets.

Registration holder's name and address:

Devries & Co. Ltd., 32 Habarzel St., Tel Aviv.

Manufacturer's name and address:

Mylan Pharma GmbH, Turmstrasse 24, 6312 Steinhausen, Switzerland

Revised in March 2021 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:

Leponex 25 mg tablets: 058 75 23147

Leponex 100 mg tablets: 047 98 23148