

PACKAGE LEAFLET: INFORMATION FOR THE USER

Leponex

25 mg tablets; 100 mg tablets

CLOZAPINE

• This leaflet is a copy of the Summary of Product Characteristics and Patient Information Leaflet for a medicine, which outlines the conditions under which the medicine should be used and information on its known safety • The product information may be updated several times within its shelf life, and there could be differences between the version of information shown here and other information in the public domain or in the package insert • This leaflet may not contain all the information about the medicine or the information may not be the most up to date version for this product • If you have any questions or are not sure about anything, ask your doctor or pharmacist • Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet • You may need to read it again • If you have any further questions, ask your doctor or pharmacist • This medicine has been prescribed for you only • Do not pass it on to others • It may harm them, even if their signs of illness are the same as yours • If you get any side effects, talk to your doctor or pharmacist • This includes any possible side effects not listed in this leaflet •

What is in this leaflet?

1. What Leponex is and what it is used for
2. What you need to know before you take Leponex
3. How to take Leponex
4. Possible side effects
5. How to store Leponex

1. WHAT LEPONEX IS AND WHAT IT IS USED FOR

The active ingredient of Leponex is clozapine which belongs to a group of medicines called antipsychotics (medicines that are used to treat specific mental disorders such as psychosis).

Leponex is used to treat people with schizophrenia in whom other medicines have not worked. Schizophrenia is a mental illness which affects how you think, feel and behave. You should only use this medicine if you have already tried at least two other antipsychotic medicines, including one of the newer atypical antipsychotics, to treat schizophrenia, and these medicines did not work, or caused severe side effects that cannot be treated.

Leponex is also used to treat severe disturbances in the thoughts, emotions and behaviour of people with Parkinson's disease in whom other medicines have not worked.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE LEPONEX

Do not take Leponex

- if you are allergic (hypersensitive) to clozapine or any of the other ingredients of Leponex.
- if you are not able to have regular blood tests.

- if you have ever been told you have a low white blood cell count (e.g. leucopenia or agranulocytosis), especially if this was caused by medicines. This does not apply if you have had low white blood cell count caused by previous chemotherapy.
- if you had to stop using Leponex previously because of severe side effects (e.g. agranulocytosis or heart problems).
- if you are being or have been treated with long-acting depot injections of antipsychotics.
- if you suffer from bone marrow disease or have ever suffered from bone marrow disease.
 - if you suffer from uncontrolled epilepsy (seizures or fits).
- if you have an acute mental illness caused by alcohol or drugs (e.g. narcotics).
- if you suffer from reduced consciousness and severe drowsiness.
- if you suffer from circulatory collapse which may occur as a result of severe shock.
- if you suffer from any severe kidney disease.
- if you suffer from myocarditis (an inflammation of the heart muscle).
- if you suffer from any other severe heart disease.
- if you have symptoms of active liver disease such as jaundice (yellow colouring of the skin and eyes, feeling sick and loss of appetite).
- if you suffer from any other severe liver disease.
- if you suffer from paralytic ileus (your bowel does not work properly and you have severe constipation).
- if you use any medicine that stops your bone marrow from working properly.
- if you use any medicine that reduces the number of white cells in your blood. If any of the above applies to you, tell your doctor and do not take Leponex.

Leponex must not be given to anyone who is unconscious or in a coma.

Warnings and Precautions

The safety measures mentioned in this section are very important. You must comply with them to minimise the risk of serious life-threatening side effects.

Before you start treatment with Leponex, tell your doctor if you suffer from or have ever suffered from:

- blood clots or family history of blood clots, as medicines like these have been associated with formation of blood clots.
- glaucoma (increased pressure in the eye).
- diabetes. Elevated (sometimes considerably) blood sugar levels, has occurred in patients with or without diabetes mellitus in their medical history (see section 4).
- prostate problems or difficulty in urinating.
- any heart, kidney or liver disease.
- chronic constipation or if you are taking medicines which cause constipation (such as anticholinergics).
- galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
- controlled epilepsy.
- large intestine diseases.
- tell your doctor if you have ever had abdominal surgery.
- if you have had a heart disease or family history of abnormal conduction in the heart called "prolongation of the QT interval".
- if you are at risk for having a stroke, for example if you have high blood pressure, cardiovascular problems or blood vessel problems in the brain.

Tell your doctor immediately before taking the next Leponex tablet:

- if you get signs of a cold, fever, flu-like symptoms, sore throat or any other infection. You will have to have an urgent blood test to check if your symptoms are related to your medicine.

- if you have a sudden rapid increase in body temperature, rigid muscles which may lead to unconsciousness (neuroleptic malignant syndrome) as you may be experiencing a serious side effect which requires immediate treatment.
- if you have fast and irregular heart beat, even when you are at rest, palpitations, breathing problems, chest pain or unexplained tiredness. Your doctor will need to check your heart and if necessary refer you to a cardiologist immediately.
- if you experience nausea (feeling sick), vomiting (being sick) and/or loss of appetite. Your doctor will need to check your liver.
- if you have severe constipation. Your doctor will have to treat this in order to avoid further complications.

Medical check-ups and blood tests

Before you start taking Leponex, your doctor will ask about your medical history and do a blood test to ensure that your white blood cells count is normal. It is important to find this out, as your body needs white blood cells to fight infections.

Make sure that you have regular blood tests before you start treatment, during treatment and after you stop treatment with Leponex.

- Your doctor will tell you exactly when and where to have the tests. Leponex may only be taken if you have a normal blood count.
- Leponex can cause a serious decrease in the number of white cells in your blood (agranulocytosis). Only regular blood tests can tell the doctor if you are at risk of developing agranulocytosis.
- During the first 18 weeks of treatment, tests are needed once a week. Afterwards, tests are needed at least once a month.
- If there is a decrease in the number of white blood cells, you will have to stop Leponex treatment immediately. Your white blood cells should then return to normal.
- You will need to have blood tests for another 4 weeks after the end of Leponex treatment.

Your doctor will also do a physical examination before starting treatment. Your doctor may do an electrocardiogram (ECG) to check your heart, but only if this is necessary for you, or if you have any special concerns.

If you have a liver disorder you will have regular liver function tests as long as you continue to take Leponex. If you suffer from high levels of sugar in the blood (diabetes) your doctor may regularly check your level of sugar in the blood.

Leponex may cause alteration in blood lipids. Leponex may cause weight gain. Your doctor may monitor your weight and blood lipid level.

If Leponex makes you feel light-headed, dizzy or faint, be careful when getting up from a sitting or lying position.

If you have to undergo surgery or if for some reason you are unable to walk around for a long time, discuss with your doctor the fact that you are taking Leponex. You may be at risk of thrombosis (blood clotting within a vein).

Children and adolescents under 16 years

If you are under 16 years of age you should not use Leponex as there is not enough information on its use in that age group.

Older people (aged 60 years and over)

Older people (aged 60 years and over) may be more likely to have the following side effects during treatment with Leponex: faintness or light-headedness after changing position, dizziness, fast heart beat, difficulty in passing urine, and constipation.

Tell your doctor or pharmacist if you suffer from a condition called dementia.

Other medicines and Leponex

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription or herbal therapies. You might need to take different amounts of your medicines or to take different medicines.

Do not take Leponex together with medicines that stop the bone marrow from working properly and/or decrease the number of blood cells produced by the body, such as:

- carbamazepine, a medicine used in epilepsy.
- certain antibiotics: chloramphenicol, sulphonamides such as co-trimoxazole.
- certain painkillers: pyrazolone analgesics such as phenylbutazone.
- penicillamine, a medicine used to treat rheumatic joint inflammation.
- cytotoxic agents, medicines used in chemotherapy.
- long-acting depot injections of antipsychotic medicines.

These medicines increase your risk of developing agranulocytosis (lack of white blood cells).

Taking Leponex at the same time as another medicine may affect how well Leponex and/or the other medicine works. Tell your doctor if you plan to take, if you are taking (even if the course of treatment is about to end) or if you have recently had to stop taking any of the following medicines:

- medicines used to treat depression such as lithium, fluvoxamine, tricyclic antidepressants, MAO inhibitors, citalopram, paroxetine, fluoxetine, and sertraline.
- other antipsychotic medicines used to treat mental illnesses such as perazine.
- benzodiazepines and other medicines used to treat anxiety or sleep disturbances.
- narcotics and other medicines which can affect your breathing.
- medicines used to control epilepsy such as phenytoin and valproic acid.
- medicines used to treat high or low blood pressure such as adrenaline and noradrenaline.
- warfarin, a medicine used to prevent blood clots.
- antihistamines, medicines used for colds or allergies such as hay fever.
- anticholinergic medicines, which are used to relieve stomach cramps, spasms and travel sickness.
- medicines used to treat Parkinson's disease.
- digoxin, a medicine used to treat heart problems.
- medicines used to treat a fast or irregular heart beat.
- some medicines used to treat stomach ulcers, such as omeprazole or cimetidine.
- some antibiotic medicines, such as erythromycin and rifampicin.
- some medicines used to treat fungal infections (such as ketoconazole) or viral infections (such as protease inhibitors, used to treat HIV infections).
- atropine, a medicine which may be used in some eye drops or cough and cold preparations.
- adrenaline, a medicine used in emergency situations.
- hormonal contraceptives (birth-control tablets).

This list is not complete. Your doctor and pharmacist have more information on medicines to be careful with or to avoid while taking Leponex. They will also know if the medicines you are taking belong to the listed groups. Speak to them.

Taking Leponex with food and drink

Do not drink alcohol during treatment with Leponex.

Tell your doctor if you smoke and how often you have drinks containing caffeine (coffee, tea, cola). Sudden changes in your smoking habits or caffeine drinking habits can also change the effects of Leponex.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the benefits and possible risks of using this medicine during pregnancy. Tell your doctor immediately if you become pregnant during treatment with Leponex.

The following symptoms may occur in newborn babies, of mothers that have used Leponex in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness,

sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Some women taking some medicines to treat mental illnesses have irregular or no periods. If you have been affected in this way, your periods might return when your medicine is changed to Leponex. This means you should use effective contraception.

Do not breast-feed during treatment with Leponex. Clozapine, the active substance of Leponex, may pass into your milk and affect your baby.

Driving and using machines

Leponex might cause tiredness, drowsiness and seizures, especially at the beginning of treatment. You should not drive or operate machines while you have these symptoms.

Leponex contains lactose.

If you have been told by your doctor that you have an intolerance to some sugars, discuss this with your doctor before taking Leponex.

3. HOW TO TAKE LEPONEX

In order to minimise the risk of low blood pressure, seizures and drowsiness it is necessary that your doctor increases your dose gradually. Always take Leponex tablets exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

It is important that you do not change your dose or stop taking Leponex without asking your doctor first. Continue taking the tablets for as long as your doctor tells you. If you are 60 years or older, your doctor may start you on a lower dose and increase it more gradually because you might be more likely to develop some unwanted side effects (see section 2 "Before you take Leponex").

If the dose you are prescribed cannot be achieved with this strength tablet, other strengths of this medicinal product are available to achieve the dose.

Treatment of schizophrenia

The usual starting dose is 12.5 mg (one half of a 25 mg tablet) once or twice on the first day followed by 25 mg once or twice on the second day. Swallow the tablet with water. If tolerated well, your doctor will then gradually increase the dose in steps of 25-50 mg over the next 2-3 weeks until a dose up to 300 mg per day is reached. Thereafter, if necessary, the daily dose may be increased in steps of 50 to 100 mg half-weekly or, preferably, at weekly intervals.

The effective daily dose is usually between 200 mg and 450 mg, divided into several single doses per day. Some people might need more. A daily dose of up to 900 mg is allowed. Increased side effects (in particular seizures) are possible at daily doses over 450 mg. Always take the lowest effective dose for you. Most people take part of their dose in the morning and part in the evening. Your doctor will tell you exactly how to divide your daily dose. If your daily dose is only 200 mg, then you can take this as a single dose in the evening. Once you have been taking Leponex with successful results for some time, your doctor may try you on a lower dose. You will need to take Leponex for at least 6 months.

Treatment of severe thought disturbances in patients with Parkinson's disease

The usual starting dose is 12.5 mg (one half of a 25 mg tablet) in the evening. Swallow the tablet with water. Your doctor will then gradually increase the dose in steps of 12.5 mg, not faster than two steps a week, up to a maximum dose of 50 mg by the end of the second week. Increases in the dosage should be stopped or postponed if you feel faint, light-headed or confused. In order to avoid such symptoms your blood pressure will be measured during the first weeks of treatment.

The effective daily dose is usually between 25 mg and 37.5 mg, taken as one dose in the evening. Doses of 50 mg per day should only be exceeded in exceptional cases. The maximum daily dose is 100 mg. Always take the lowest effective dose for you.

If you take more Leponex than you should

If you think that you may have taken too many tablets, or if anyone else takes any of your tablets, contact a doctor immediately or call for emergency medical help.

The symptoms of overdose are:

Drowsiness, tiredness, lack of energy, unconsciousness, coma, confusion, hallucinations, agitation, incoherent speech, stiff limbs, trembling hands, seizures (fits), increased production of saliva, widening of the black part of the eye, blurred vision, low blood pressure, collapse, fast or irregular heart beat, shallow or difficult breathing.

If you forget to take Leponex

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, leave out the forgotten tablets and take the next dose at the right time. Do not take a double dose to make up for a forgotten dose. Contact your doctor as soon as possible if you have not taken any Leponex for more than 48 hours.

If you stop taking Leponex

Do not stop taking Leponex without asking your doctor, because you might get withdrawal reactions. These reactions include sweating, headache, nausea (feeling sick), vomiting (being sick) and diarrhoea. If you have any of the above signs, tell your doctor straight away. These signs may be followed by more serious side effects unless you are treated immediately. Your original symptoms might come back. A gradual reduction in dose in steps of 12.5 mg over one to two weeks is recommended, if you have to stop treatment. Your doctor will advise you on how to reduce your daily dose. If you have to stop Leponex treatment suddenly, you will have to be checked by your doctor.

If your doctor decides to re-start the treatment with Leponex and your last dose of Leponex was over two days ago, this will be with the starting dose of 12.5 mg.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Leponex can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention: Tell your doctor immediately before taking the next Leponex tablet:

Very common (affects more than 1 in 10 people):

- if you have severe constipation. Your doctor will have to treat this in order to avoid further complications.

Common (affects up to 1 in 10 people):

- if you get signs of a cold, fever, flu-like symptoms, sore throat or any other infection. You will have to have an urgent blood test to check if your symptoms are related to your medicine.
- if you experience seizures.

Uncommon (affects up to 1 in 100 people):

- if you have a sudden rapid increase in body temperature, rigid muscles which may lead to unconsciousness (neuroleptic malignant syndrome) as you may be experiencing a serious side effect which requires immediate treatment.

Rare (affects up to 1 in 1,000 people):

- if you get signs of a respiratory tract infection or pneumonia such as fever, coughing, difficulty breathing, wheezing.
- if you experience nausea (feeling sick), vomiting (being sick) and/or loss of appetite. Your doctor will need to check your liver.

Rare (affects up to 1 in 1,000 people) **or very rare** (affects up to 1 in 10,000 people):

- if you have fast and irregular heart beat, even when you are at rest, palpitations, breathing problems, chest pain or unexplained tiredness. Your doctor will need to check your heart and if necessary refer you to a cardiologist immediately.

Very rare (affects up to 1 in 10,000 people):

- if you are a man and experience persistent painful erection of the penis. This is called priapism. If you have an erection which lasts more than 4 hours immediate medical treatment may be needed in order to avoid further complications.

Unknown (frequency cannot be estimated from the available data)

- if you experience crushing chest pain, sensation of chest tightness, pressure or squeezing (chest pain may radiate to the left arm, jaw, neck and upper abdomen), shortness of breath, sweating, weakness, light headedness, nausea, vomiting and palpitations (symptoms of heart attack). You should seek emergency medical treatment immediately.
- if you experience chest pressure, heaviness, tightness, squeezing, burning or choking sensation (signs of insufficient blood flow and oxygen to the heart muscle). Your doctor will need to check your heart.
- if you get signs of blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing.
- if you experience profuse sweating, headache, nausea, vomiting and diarrhoea (symptoms of cholinergic syndrome).
- if you experience severely decreased urine output (sign of kidney failure).
- if you experience an allergic reaction (swelling mainly of the face, mouth and throat, as well as, the tongue, which may be itchy or painful).

If any of the above apply to you, please tell your doctor immediately before taking the next Leponex tablet.

Other side effects:

Very common (affects more than 1 in 10 people):

Drowsiness, dizziness, fast heart beat, increased production of saliva.

Common (affects up to 1 in 10 people):

High level of white blood cells (leukocytosis), high level of a specific type of white blood cell (eosinophilia), weight gain, blurred vision, headache, trembling, stiffness, restlessness, convulsions, jerks, abnormal

movements, inability to initiate movement, inability to remain motionless, changes in ECG heart machine, high blood pressure, faintness or light-headedness after changing position, sudden loss of consciousness, nausea (feeling sick), vomiting (being sick), loss of appetite, dry mouth, minor abnormalities in liver function tests, loss of bladder control, difficulty in passing urine, tiredness, fever, increased sweating, raised body temperature, speech disorders (e.g. slurred speech).

Uncommon (affects up to 1 in 100 people):

Lack of white blood cells (agranulocytosis), speech disorders (e.g. stuttering).

Rare (affects up to 1 in 1,000 people):

Low level of red blood cells (anaemia), restlessness, agitation, confusion, delirium, circulatory collapse, irregular heart beat, inflammation of the heart muscle (myocarditis) or the membrane surrounding the heart muscle (pericarditis), fluid collection around the heart (pericardial effusion), difficulty in swallowing (e.g. food going down the wrong way), high level of sugar in the blood, diabetes mellitus, blood clot in the lungs (thromboembolism), inflammation of the liver (hepatitis), liver disease causing yellowing of the skin/dark urine/itching, inflammation of the pancreas leading to severe upper stomach pain, raised levels of an enzyme called creatinine phosphokinase in the blood.

Very rare (affects up to 1 in 10,000 people):

Increase in numbers of blood platelets with possible clotting in the blood vessels, decrease in numbers of blood platelets, uncontrollable movements of mouth/tongue and limbs, obsessive thoughts and compulsive repetitive behaviours (obsessive compulsive symptoms), skin reactions, swelling in front of the ear (enlargement of saliva glands), difficulty in breathing, complications due to uncontrolled blood sugar (e.g. coma or ketoacidosis), very high levels of triglycerides or cholesterol in the blood, disorder of the heart muscle (cardiomyopathy), stopped heart beat (cardiac arrest), severe constipation with abdominal pain and stomach cramps caused by obstruction of the bowel (paralytic ileus), swollen abdomen, abdominal pain, severe liver damage (fulminant hepatic necrosis), inflammation of the kidneys, sudden unexplained death.

Unknown (frequency cannot be estimated from the available data)

Liver disorders including fatty liver disease, death of liver cells, liver toxicity/injury, liver disorders that involve replacement of normal liver tissue with scar tissue leading to loss of liver function, including those liver events leading to life-threatening consequences such as liver failure (which may lead to death), liver injury (injury of liver cells, bile duct in the liver, or both) and liver transplant, changes in brain waves machine (electroencephalogram/EEG), diarrhoea, stomach discomfort, heartburn, stomach discomfort after a meal, muscle weakness, muscle spasms, muscle pain, stuffy nose, nocturnal bedwetting, sudden, uncontrollable increase in blood pressure (pseudophaeochromocytoma), uncontrolled bending of the body to one side (pleurothotonus), ejaculatory disorder if you are a male, in which semen enters the bladder instead of ejaculating through the penis (dry orgasm or retrograde ejaculation), rash, purplish-red spots, fever or itching due to inflammation of blood vessel, inflammation of the colon resulting in diarrhoea, abdominal pain, fever, change in skin colour, "butterfly" facial rash, joint pain, muscle pain, fever and fatigue (lupus erythematosus).

In elderly people with dementia, a small increase in the number of people dying has been reported for patients taking antipsychotics compared with those not taking antipsychotics.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE LEPONEX

Keep this medicine out of the sight and reach of children.

Do not use Leponex after the expiry date which is stated on the blister/bottle and the carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

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