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רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

אוקטובר 2020

**Leponex 25 mg tablets**
**Leponex 100 mg tablets**

חברת דיפריס ושות' בע"מ מבקשת להודיע על עדכון בעלון לרופא של התכשיר שבנדון.

**ההתוויה הרשומה של התכשיר בישראל:**

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.

**צורת המתן של התכשיר :** טבליות לבליעה

**מרכיב פעיל:**

Clozapine 25 mg, Clozapine 100 mg

בהודעה זו מצוינים סעיפים בהם נעשה עדכון המהווה החמרה - מודגש בצהוב.
בעלון נעשו עדכונים נוספים על העדכונים המצויינים כאן.

### 4.2. Posology and method of administration

**Method of Administration**

**Treatment-resistant schizophrenia**

Starting therapy

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

Maximum dose

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.

### 4.3 Contraindications

- Acute liver disease associated with nausea, loss of appetite or jaundice; progressive liver disease; hepatic failure.

### 4.4 Warnings and precautions

In the event of infection, antibiotic therapy must be initiated immediately due to the risk of septic shock

*Cardiotoxicity*

Before starting treatment with clozapine, run an ECG and verify that there are no conduction abnormalities.

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.
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).
*Myocarditis and cardiomyopathy*
…
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.
*Seizures*
If a patient has epilepsy, make sure that an anticonvulsant is used at a therapeutic level and consult with a neurologist if needed.
*Risk of thromboembolism*
Immobilisation must be avoided since Leponex may cause sedation and weight gain, thus increasing the risk of thromboembolism.
*Anticholinergic effects*
bowel perforation
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.

Special precautions should be observed when considering co-administration with benzodiazepines (or other centrally-acting drugs; see "Interactions").
*Metabolic changes*
Treatment with clozapine leads to weight gain at a higher ratio than with all other antipsychotics and to a higher incidence of metabolic symptoms.
*Diabetes*
Diabetes may develop among clozapine patients at a higher incidence than among the general population.
*Psychosis/behavioural disorders in elderly patients with dementia*
Leponex is not approved for the treatment of psychosis/behavioural disorders in elderly patients (≥60 years) with dementia.

### 4.5 Interactions with other medicinal products and other forms of interaction
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).

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.

It is recommended to avoid administering medicines to lower blood pressure that are ACE inhibitors, antihistamines and barbiturates concomitantly with clozapine.

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.

- 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 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.

*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:*

- 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).

## 4.6 Fertility, pregnancy and breast-feeding

*Pregnancy*

Certain toxic effects have been observed in animal studies (see “Preclinical data”). No clinical data is available on use in pregnant women.

*Non-teratogenic effects*

If discontinuation of treatment is required during pregnancy, it should not be done abruptly.

## 4.8 Undesirable effects

*Blood and lymphatic system disorders*

*Rare:* Lymphopenia.

*Very rare:* thrombocytosis, anaemia.

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.

*Nervous system disorders*

*Rare:* Confusion… Fatal convulsions have been reported.

*Cardiac disorders*

*Very common:* Tachycardia (particularly in the first weeks of treatment with Leponex; 25%).

ECG changes (ST segment depression, flattening and inversion of the T wave, conduction disturbances) may frequently occur.

*Vascular disorders*

*Rare:* including fatal cases and cases occurring in combination with organ necrosis (e.g. intestine);

*Hepatobiliary disorders*

*Rare:* jaundice

*Renal and urinary disorders*

*Very rare:* renal impairment, renal failure.

*Reproductive system and breast disorders*

*Very rare:* impotence, changes in ejaculation, dysmenorrhoea.

*Investigations*

*Very rare:* Hyponatraemia.

*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)*
*Infections and infestations*
Sepsis.
*Immune system disorders*
Drug rash with eosinophilia and systemic symptoms (DRESS),
*Metabolism and nutrition disorders*
Obesity.
*Nervous system disorders*
restless legs syndrome (RLS)
*Cardiac disorders*
palpitations, atrial fibrillation, mitral valve incompetence associated with Leponex-related cardiomyopathy.
*Vascular disorders*
Hypotension.
*Respiratory, thoracic and mediastinal disorders*
Pleural effusion, sleep apnoea syndrome
*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,
*Musculoskeletal and connective tissue disorders*
Rhabdomyolysis,
*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).

**4.9 Overdose**

Massive overdose, whether accidental or with suicidal intent, represents a serious danger to the patient.
*Signs and symptoms*
cardiac arrhythmia (in particular, AV block and extrasystoles), impaired cardiac conduction;

*Treatment*
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).