# Patient leaflet in accordance with the Pharmacists' Regulations (Medicinal Products) - 1986

**This medicine is dispensed with a doctor's prescription only**

## RECORLEV® 150 mg

**Tablets for oral use**

**Active ingredient:** Each tablet contains Levoketoconazole 150 mg.

For the list of excipients and allergens in the medicinal product, please see section 2: "Important information regarding some of the ingredients of the medicine" and section 6: "Additional information".

**Read the entire leaflet carefully before you start using the medicine.** This leaflet contains concise information about the medicine. If you have any further questions, contact the physician or the pharmacist.

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

**WARNING: HEPATOTOXICITY AND QT PROLONGATION**

**Hepatotoxicity**

- **Cases of hepatotoxicity with a fatal outcome or requiring liver transplantation have been reported with use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Serious hepatotoxicity has been reported in patients receiving RECORLEV.**
- **RECORLEV is contraindicated in patients with cirrhosis, acute liver disease or poorly controlled chronic liver disease, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease.**
- **Evaluate liver enzymes prior to and during treatment. Interrupt RECORLEV treatment immediately if signs of hepatotoxicity occur.**

**QT Prolongation**

- **RECORLEV is associated with dose-related QT interval prolongation. QT interval prolongation may lead to life-threatening ventricular dysrhythmias such as torsades de pointes.**
- **Coadministration of RECORLEV with other drugs that prolong the QT interval associated with ventricular arrhythmias, including torsades de pointes, and use in patients with a prolonged QTcF interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history) are contraindicated.**
- **Perform an ECG and correct hypokalemia and hypomagnesemia prior to and during treatment. Temporarily discontinue RECORLEV if QTcF interval exceeds 500 msec.**

## 1. What is the medicine intended for?

RECORLEV is indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.

Limitations of Use

RECORLEV is not approved for the treatment of fungal infections. The safety and effectiveness of RECORLEV for the treatment of fungal infections have not been established.

**Therapeutic group:** Anticorticosteroids (cortisol synthesis inhibitor)

## 2. Before using this medicine:

**Do not use the medicine if:**

- You are hypersensitive (allergic) to levoketoconazole, ketoconazole or any of the additional ingredients that this medicine contains (see section 6 – "additional information").
- You have cirrhosis.
- You have an active or poorly controlled liver disease, including elevated liver enzymes.
- You have frequent stones in your gallbladder (cholelithiasis).
- You have a history of liver problems due to use of ketoconazole or any azole antifungal therapy that required discontinuation of treatment.
- You have extensive metastatic liver disease.
- You are taking certain other medicines that cause QT prolongation.
- You have a history of certain heart problems which may include one the following conditions: torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome.
- You are taking certain medicines that may affect how your liver works (for example, CYP3A4 or P-gP inhibitors). If you are not sure if you take these medicines, please ask your healthcare provider. For additional information please see section 2 – " drug interactions" and section 4 – "side effects").

**Special warnings regarding the use of this medicine:**

**Before taking Recorlev, tell your doctor if**:

- you have or have had liver problems.
- you have any heart problems, including a condition called long QT syndrome.
- you have a history of low blood levels of potassium or magnesium.
- you are pregnant or plan to become pregnant. RECORLEV may harm your baby.
- you are breastfeeding or plan to breastfeed. RECORLEV can pass into your breast milk.

Liver damage (hepatotoxicity)

Hepatotoxicity can happen in people who take RECORLEV. Some people who are treated with ketoconazole, a medicine like the active ingredient in RECORLEV, had serious liver problems that required a liver transplant or led to death.

Refer to your healthcare provider right away if you have any of the following signs or symptoms:

- pain on the upper right side of your stomach area (abdomen) associated with nausea
- unusual fatigue

- yellowing of your skin or the whites of your eyes (jaundice)
- unusual bruising or bleeding

Heart rhythm problems (QT prolongation)

RECORLEV can cause a heart problem called QT interval prolongation, or QT prolongation. QT prolongation can cause irregular heartbeats that can be life threatening.

Refer to healthcare provider right away if you feel severe lightheadedness or if you faint during treatment with RECORLEV. Low blood electrolyte levels of potassium and magnesium can increase your chances of QT prolongation during treatment with RECORLEV.

Low cortisol levels (adrenal insufficiency)

Adrenal insufficiency is a condition in which the adrenal glands do not make enough steroid hormones, such as cortisol. RECORLEV may cause adrenal function insufficiency by excessively lowering production of cortisol.

Refer to your healthcare provider right away if you have one or more of the following symptoms, as these may be symptoms of reduced adrenal function:

- nausea/vomiting
- dizziness
- unusual fatigue
- low blood pressure (hypotension)
- unexplained stomach pain (abdomen)
- abnormal electrolyte levels
- loss of appetite
- low blood sugar (hypoglycemia)
- body aches

Hypersensitivity reactions

Serious allergic reactions can happen in people who take RECORLEV. Refer to your healthcare provider right away, or visit an emergency center, if you get a rash, itching, hives, fever, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.

Risks related to decreased testosterone

RECORLEV may lower testosterone levels in males and females. Refer to your healthcare provider if you have any of these symptoms:

- Males: breast enlargement (gynecomastia) and erectile dysfunction (impotence)
- Females: low desire for sex (decreased libido) and mood changes.

**Children and adolesence:**

This medicine is not indicated for children and adolesence below the age of 18, the safety and effectiveness of RECORLEV in patients below the age of 18 have not been established.

**Tests and follow-up:**

- Your healthcare provider will do liver tests before and during treatment with RECORLEV.
- Your healthcare provider will check your heart using electrocardiogram (ECG) and do blood tests to check your blood electrolyte levels before and during treatment with RECORLEV.
- Your healthcare provider will collect blood or urine samples periodically during RECORLEV treatment to measure your cortisol.

**Drug interactions:**

**If you are taking, or have recently taken, other medicines including non-prescription medicines and nutritional supplements, tell your doctor or pharmacist.**

RECORLEV should not be taken with certain other medicines that cause QT prolongation. Talk to your healthcare provider about the medicines you are taking before you start taking RECORLEV.

RECORLEV and other medicines may affect each other causing side effects. RECORLEV may affect the way other medicines work, and other medicines may affect how RECORLEV works.

RECORLEV is a CYP3A4, P-gp, OCT2, MATE1 inhibitor and concomitant use with drugs that are substrates of CYP3A4 and mentioned transporters (for exemple Atorvastatin to reduce cholesterol levels or Metformin to treat diabetes) may increase plasma concentration of the substrate and the risk for the substrate's advese reactions.

Drugs that inhibit CYP3A4 (for example antiviral medicines, glucocorticoid and progesterone receptor antagonists) may increase Levoketoconazole levels and the risk of adverse reactions from RECORLEV.

Drugs that induce CYP3A4 (for example antibacterials, anticonvulsants, antivirals and cytotoxic agents) may decrease Levoketoconazole levels and reduce the efficacy of RECORLEV.

Gastric acid neutralizers (for example aluminum hydroxide) impairs Levoketoconazole absorption and therefore should be taken at least two hours after taking RECORLEV.

Gastric acid suppressors (for example H2-receptor antagonists and proton pump inhibitors) and sucralfate impair Levoketoconazole absorption and therefore you should avoid concomitant use with RECORLEV. **Use of the medicine and food**:

RECORLEV can be taken with or without food.

**Use of the medicine and alcohol consumption:**

Drinking alcohol to excess while taking RECORLEV may increase your chances of having serious side effects.

**Pregnancy, breast-feeding and fertility:**

Pregnancy

Tell your healthcare provider if you are pregnant or plan to become pregnant. RECORLEV may harm your baby. Tell your healthcare provider right away if you become pregnant during treatment with RECORLEV or think you might be pregnant.

Breast-feeding

Tell your healthcare provider if you are breastfeeding or plan to breastfeed. RECORLEV can pass into your breast milk. You and your healthcare provider should decide if you should take RECORLEV or breastfeed. You should not breastfeed during treatment with RECORLEV and for 1 day after the final dose.

Fertility

RECORLEV may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

**Driving and using machines:**

RECORLEV may have a moderate influence on the ability to drive and use machines. Do not drive or operate machines if you experience dizziness or fatigue.

**Important information regarding some of the ingredients of the medicine:**

This medicine contains Lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 3. How to use the medicine?

Always use the medicinal product according to the doctor's instructions.

Check with your doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicinal product.

The dosage and treatment regimen will be determined only by the doctor.

The commonly recommended starting dose is 1 tablet taken by mouth 2 times a day, with or without food. The maximum recommended dosage is 4 tablets taken twice a day.

Your healthcare provider may decrease, temporarily hold, or permanently stop your treatment with RECORLEV if needed.

**Do not exceed the recommended dose.**

There is no information concerning crushing/splitting/chewing of the tablets.

**If you have taken more RECORLEV than you should**, consult with your healthcare provider or go to the nearest hospital emergency room right away and bring the drug package with you.

**If you forget to take the medicine,** take the next dose at your regular scheduled time. **Do not take a double dose.**

You should continue the treatment as recommended by the doctor. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

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

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

## 4. Side effects

As with any medicine, RECORLEV can cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

RECORLEV may cause serious side effects, seek immediate medical attention if you develop any of the following severe side effects:

- Liver damage (hepatotoxicity)
- Heart rhythm problems (QT prolongation)
- Low cortisol levels (adrenal insufficiency)
- Hypersensitivity reactions
- Risks related to decreased testosterone

For further information please see section 2 "Special warnings regarding the use of this medicine".

**Very common side effects – may affect more than 1 in 10 people:**

- Nausea/Vomiting
- Hypokalemia (low potassium)
- High blood pressure
- Hemorrhage (easy bleeding)/contusion (easy bruising)
- Headache
- Hepatic Injury
- Elevated liver function tests
- Abnormal uterine bleeding

- Erythema (redness of the skin)
- Abnormal heart rhythm
- Fatigue
- Arthritis
- Upper respiratory infection
- Myalgia (muscle pain)
- Abdominal pain/dyspepsia (upset stomach)
- Dizziness
- Diarrhea
- Decreased appetite
- Dry mouth
- Dry skin
- Back pain
- Insomnia/Sleep disturbances
- Peripheral edema (fluid retention)
- Pre-Syncope/Syncope
- Rash
- Urinary tract infections
- Pruritus
- Disturbance in attention
- Irritability
- Depression
- Alopecia

**Common side effects – may affect 1-10 out of 100 people:**

- Adrenal insufficiency
- Gastrointestinal infections
- Hypogonadism
- Hypersensitivity
- Decreased libido
- Gynecomastia

**If a side effect appears, if any side effect gets worse or if you suffer from a side effect not mentioned in the leaflet, you should consult the doctor.**

**Reporting of side effects:**

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il) which links to an online form for reporting side effects, or by the following link: https://sideeffects.health.gov.il/ and by emailing the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

## 5. How to store the medicine?

* Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the sight and reach of children and/or infants to avoid poisoning. Do not induce vomiting without specific instruction from the doctor.

* Do not use the medicine after the expiration date (exp. date) appearing on the packaging. The expiration date refers to the last day of that month.

* Store below 25°C.

* After opening the bottle, the medicine can be used for up to 3 months when stored at room temperature (below 25°C).

## 6. Additional information

**In addition to the active ingredient(s), the medicine also contains:**

lactose monohydrate, silicified microcrystalline cellulose, modified corn starch, magnesium stearate and colloidal silicon dioxide.

The pink film-coating contains:

polyvinyl alcohol partially hydrolyzed, titanium dioxide, macrogol/polyethylene glycol 3350, talc and iron oxide red.

The tablets are printed with a black imprinting ink that contains:

shellac glaze 45% (20% esterified) in ethanol, ferrosoferric oxide, isopropyl alcohol, propylene glycol and ammonium hydroxide 28%.

**What does the medicine look like and the contents of the package:**

RECORLEV is a round, biconvex tablets, with a pink- colored film coating imprinted with an identification code "LEV 150" on one side in black ink.

The bottle has a child resistant closure.

Each bottle contains 50 tables.

**Manufacturer**:

XERIS PHARMACEUTICALS, Inc.,

Chicago, IL 60607, USA.

**Registration Holder:**

NEOPHARM Ltd.,

Hashiloach 6, POB 7063, Petach Tikva 4917001, Israel.

**Registration number of the medicine in the National Drug Registry of the Ministry of Health:** 174-69-37497-99

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