PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Ketoconazole HRA 200 mg tablets

Each Ketoconazole HRA 200 mg tablet contains:
Ketoconazole 200 mg

For a list of inactive ingredients in the preparation - see section 6.

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the doctor or the pharmacist.

This medicine has been prescribed for treatment of your illness. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.
The medicine is not intended for children under the age of 12.

1. What is the medicine intended for?

Ketoconazole HRA is used to treat endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.
Therapeutic class: Imidazole derivatives.

2. Before using the medicine:

X Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient ketoconazole and\or to any imidazole antifungal, or to any of the other ingredients (see section 6 - Additional Information).
- You are suffering from liver problems.
- You are pregnant.
- You are breastfeeding.
- You have a history of an irregular heartbeat.
- You are taking any of the following medicines:
    - Certain medicines for lowering blood cholesterol: simvastatin, atorvastatin, lovastatin.
    - Certain heart medicines: eplerenone, dronedarone, disopyramide, felodipine, nisoldipine, ranolazine.
    - Certain medicines used for treatment of the paludism: quinidine, halofantrine.

- Certain medicines used for treatment of severe mental health disorders and severe depression: pimozide, sertindole, lurasidone, quetiapine.
- Certain medicines used for treatment of allergies: mizolastine.
- Dabigatran - a medicine used to prevent the formation of blood clots.
- Certain medicines for sleep induction and treatment of anxiety: triazolam, alprazolam, midazolam (administered orally).
- Certain medicines used for treatment of migraine attacks: dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).
- Certain medicines used for cancer treatment: irinotecan, everolimus.
- Sirolimus: used to prevent organ rejection after transplantation.
- Tolvaptan: used for treatment of syndrome of inappropriate antidiuretic hormone secretion.
- Vardenafil (for men older than 75 years) – medicine to treat erectile dysfunction.
- Certain medicines for treatment of AIDS: saquinavir/ritonavir, saquinavir.
- Certain medicines for treatment of long-term (chronic) hepatitis C (an infectious disease that affects the liver, caused by the hepatitis C virus): paritaprevir/ombitasvir (ritonavir).
- Methadone: medicine to treat drug dependence.
- In patients with renal disorders:
  - Colchicine: medicine to treat gout.
  - Fesoterodine and solifenacin: medicines to treat the symptoms of an overactive bladder.
  - Telithromycin and clarithromycin: medicines used to treat infections.

! Special warnings regarding the use of the medicine:
Before taking Ketoconazole HRA, tell your doctor if:

- You have a history of liver disease. Your liver enzyme levels will be regularly monitored before starting the treatment and during the treatment, once a week during the first month of the treatment and then monthly for 6 months due to the risk of serious hepatic toxicity. Your liver enzymes levels will be checked again in case your doctor decides to increase your prescribed dose of ketoconazole.
  You should stop the treatment and contact your doctor immediately if you feel unwell or experience symptoms such as lack of appetite, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine.
- You are taking glucocorticoid replacement therapy concomitantly with your Ketoconazole HRA treatment, and you are under stress, planned for a surgery or have an infection. Your doctor will inform you how to adjust the

dosage of glucocorticoids you are taking. In addition, you should have an emergency glucocorticoid set.
- You are suffering from inflammatory/autoimmune disorders. As a result, you will be closely supervised during the treatment.

! Additional warnings:
- Your adrenal function will be monitored during the treatment at regular intervals, as this is the standard care in the follow-up of Cushing's syndrome therapy, since adrenal insufficiency can occur during the treatment. You should contact your doctor immediately if you have symptoms such as weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure.
- Ketoconazole HRA may change your heartbeat, which may be a serious issue. **Contact your doctor immediately if during the course of your treatment you experience palpitations or an irregular heartbeat.**

! Children and adolescents:
This medicine is not recommended for children under 12 years due to the lack of data in such patients.

! Tests and follow-up:
Before your start the treatment and during the treatment you will undergo blood tests, in order to detect any possible abnormalities in their results, and also to measure the levels of cortisol. The dose will be adjusted to your condition to restore normal cortisol levels.

! Drug-drug interactions:
If you are taking or have recently taken other medicines including non-prescription medicines and dietary supplements, tell the doctor or the pharmacist. There are some medications that must not be taken with Ketoconazole HRA (see the beginning of the section - "Do not use the medicine if"). Especially inform the doctor or pharmacist if you are taking:
- A medicine called pasireotide which is also taken for treatment of Cushing's syndrome. This is because concomitant use may lead to severe side effects in patients suffering from cardiac disorders.
- Orally administered medicines that prevent blood clots from forming: rivaroxaban, apixaban, edoxaban, cilostazol, warfarin (Coumadin) and other coumarin-like medicines.
- AIDS medicines such as maraviroc, indinavir, nevirapine, ritonavir.
- Certain medicines used for cancer treatment, such as vinca alkaloids, busulfan, docetaxel, erlotinib, imatinib, dasatinib, sunitinib, lapatinib, nilotinib, bortezomib, paclitaxel, vincristine, vinblastine, cabozantinib, dabrafenib, cabazitaxel, crizotinib, ibrutinib.
- Certain medicines used to treat infections: rifabutin, telithromycin, rifampicin, isoniazid, clarithromycin, isavuconazole.
- Certain antidiabetics: repaglinide, saxagliptin, tolbutamide.

- Certain medicines used for treatment of mental disorders: buspirone, aripiprazole, haloperidol, reboxetine, risperidone.
- Certain heart medicines: verapamil, digoxin, nadolol, aliskiren.
- Certain anticonvulsants: carbamazepine, phenitoin.
- Certain glucocorticoids – such as: budesonide, fluticasone, dexamethasone, methylprednisolone, ciclesonide.
- Certain strong painkillers (narcotics) – such as: alfentanyl, fentanyl, buprenorphine (injection and sublingual tablets), oxycodone.
- Certain medicines used for treating nausea and vomiting: domperidone, aprepitant.
- Naloxegol (medicine for treatment of constipation caused by strong pain medicines).
- Solifenacin, fesoterodine in patients with renal disorders.
- Other medicines: sildenafil, tolterodine, mitotane, praziquantel, eletriptan, salmeterol, bosentan, midazolam (by injection), tadalafil, vardenafil, temsirolimus, cinacalcet, tacrolimus, ebastine, ciclosporine, colchicine.

Do not take antacids (e.g. aluminum hydroxide) or other medicines for acid indigestion for at least 2 hours after the intake of Ketoconazole HRA.

! Use of the medicine and alcohol consumption:
Do not drink alcohol while taking Ketoconazole HRA.

! Pregnancy, breastfeeding and fertility:
Do not take this medicinal product during pregnancy. If you are pregnant or breastfeeding, think you are pregnant or are planning to become pregnant, consult with your doctor or pharmacist before taking the medicine.
Do not breastfeed if you are taking Ketoconazole HRA.

! Driving and operating machinery:
Since side effects of dizziness or somnolence have been reported during treatment with Ketoconazole HRA, do not drive or operate dangerous machines while using the medicine if you experience these side effects.

! Important information about some ingredients of the medicine:
Each tablet contains 19 mg lactose.
If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How should you use the medicine?

Always use the preparation according to the doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the preparation.
The dosage and treatment regimen will be determined by the doctor only.
Initiation and follow-up of the treatment must be supervised by a specialist in endocrinology.

The generally accepted dosage is: an initial dose of 600 mg per day (3 tablets per day: one tablet 3 times a day). A daily dose from 400 mg per day (2 tablets) to 1,200 mg per day (6 tablets) in 2 or 3 doses may be required to restore your normal cortisol levels.
Do not exceed the recommended dose.

Do not chew; the tablet is intended to be swallowed. No information is available regarding halving/pulverizing/crushing the tablet.

If you accidentally take a higher dosage
If you took an overdose or a child accidentally swallowed this medicine, go to the doctor or the emergency room of the hospital immediately and take the package of the medicine with you.

If you forget to take the medicine on time, take the next dose as soon as you remember, and go on with regular schedule as prescribed. Do not take a double dose in order to compensate for a forgotten dose. Do not change the prescribed dose yourself.

If you stop taking the medicine
If you interrupt your treatment with Ketoconazole HRA, your cortisol levels may increase again and your symptoms may come back. Therefore, do not stop taking Ketoconazole HRA unless your doctor tells you.

Follow 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 <u>every time</u> you take the medicine. Wear glasses if you need them.

If you have any other questions regarding use of the medicine, consult the doctor or the pharmacist.

4. Side effects:

Like all medicines, using Ketoconazole HRA may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

Some side effects may be serious. Liver problems can rarely happen (may affect up to 1 in 1,000 people).
Stop using this medicine and refer to a doctor immediately if you are sensing one of the following effects:

- Long-lasting severe headache or blurred vision.

- Severe lack of appetite (anorexia).
- Weight loss.
- Nausea or vomiting.
- Unusual tiredness or fever.
- Abdominal pain.
- Muscle weakness.
- Yellowing of the skin or of whites of the eyes.
- Unusually dark urine or pale stools.

Adrenal insufficiency is common and can be a serious side effect. Ketoconazole HRA may temporarily lower the amount of hormones produced by your adrenal gland (cortisol) below the normal range but your doctor will correct this by using appropriate hormone medication or by adjusting the dose of Ketoconazole HRA. You should contact your doctor immediately if you have symptoms such as weakness, fatigue, loss of appetite, nausea, vomiting, low blood pressure.

Very common side effects - side effects that occur in more than one out of ten patients:
- Elevated levels of liver enzymes in your blood.

Common side effects - side effects that occur in up to one out of ten patients:
- Nausea.
- Abdominal pain.
- Vomiting.
- Diarrhea.
- Skin reactions (pruritus, rash).

Uncommon side effects - side effects that occur in 1 out of 100 patients:
- Allergic reactions which can, rarely, be serious.
- Changes in laboratory markers.
- Decreased platelet count.
- Headache.
- Dizziness.
- Somnolence.
- Skin reactions (urticarial).
- Hair loss.
- Tiredness.

Very rare side effects - side effects that occur in 1 out of 10,000 patients:
- Fever.

Side effects occurring at an unknown frequency:
- Insomnia.
- Nervousness.

- Intolerance to alcohol.
- Loss of appetite or increased appetite.
- Headache.
- Sensation of tingling or pricking.
- Aversion to light.
- Nose bleeding.
- Digestive difficulties.
- Swelling in the stomach (flatulence).
- Tongue discoloration.
- Dry mouth.
- Distortion of the sense of taste.
- Redness, dryness or itching in the skin.
- Sensitivity to light (increased response to sunlight: redness, itchy rash).
- Myalgia (muscle pain).
- Arthralgia (joint pain).
- Menstrual disorders.
- Azoospermia (no sperm count).
- Erectile dysfunction.
- Gynaecomastia (enlargement of breast tissues in males).
- Peripheral oedema (dropsy in extremities).
- Malaise.
- Hot flashes.
- Transient decrease of testosterone, a male hormone (androgen) made by the body, mostly produced in the testes.

If a side effect occurs, or if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Reporting side effects

Side effects may be reported to the Ministry of Health by clicking on the link "report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link:
https://sideeffects.health.gov.il/

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
- Do not use the medicine after the expiry date (EXP) appearing on the package. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions. It is recommended to store the medicine in room temperature.

6. Additional information

In addition to the active ingredient, the medicine also contains:
Maize starch, lactose monohydrate, povidone K-25, microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate.

What does the medicine look like and what are the contents of the package:
A round, biconvex, off-white to light cream colored tablet.
Each pack contains 60 tablets.

License holder/importer and the address: CTS Ltd., 4 Haharash St., Hod Hasharon.

Name and address of the manufacturer:
HRA Pharma Rare Diseases, 200 avenue de Paris, 92320 Chatillon, France

This leaflet was revised in July 2021 in accordance with the Ministry of Health guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 160-67-35337