Package leaflet: Information for the patient

Ketoconazole HRA 200 mg tablets
ketoconazole

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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. See section 4.

What is in this leaflet

1. What Ketoconazole HRA is and what it is used for

Ketoconazole HRA is a medicine that contains the active substance ketoconazole. It is used to treat endogenous Cushing's syndrome (when the body produces an excess of cortisol) in adults and adolescents above the age of 12 years.

Cushing's syndrome is caused by overproduction of a hormone called cortisol which is produced by the adrenal glands. Ketoconazole HRA is able to block the activity of the enzymes responsible for the synthesis of cortisol and consequently is able to decrease the over-production of cortisol by your body and to improve the symptoms of Cushing's syndrome.

2. What you need to know before you take Ketoconazole HRA

Do not take Ketoconazole HRA

- if you are allergic to ketoconazole and/or to any imidazole antifungal medicine, or to any of the other ingredients of this medicine (listed in section 6)
- if you have liver problems
- if you are pregnant
- if you are breastfeeding
- if you have a history of an irregular heart beat
- if you are taking any of the following medicines:
    - certain medicines for lowering blood cholesterol: simvastatin, atorvastatin, lovastatin
    - certain heart medicines: epleronone, dronedarone, disopyramide, felodipine, nisoldipine, ranolazine

- certain medicines used for the treatment of the paludism: quinidine, halofantrine
- certain medicines used for severe mental health disorders and severe depression: pimozide, sertindole, lurasidone, quetiapine
- certain medicines used for the allergies: mizolastine
- dabigatran – medicine used to prevent the formation of blood clots
- certain medicines to help to sleep and for anxiety: triazolam, alprazolam, midazolam (taken by mouth)
- certain medicines used for migraine attacks: dihydroergotamine, ergometrine (ergonovine) ergotamine and methylergometrine (methylergonovine)
- certain medicines used in cancers: irinotecan, everolimus
- sirolimus: used to prevent your body from rejecting a kidney transplant
- tolvaptan used for a specific disease called "syndrome of inappropriate antidiuretic hormone secretion"
- vardenafil in men older than 75 years – medicine to treat erectile dysfunction in adults men
- certain medicines for HIV: saquinavir/ritonavir, saquinavir
- certain medicines to treat 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 dependence to drugs
- 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: medicine used to treat infections

Do not take Ketoconazole HRA if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Ketoconazole HRA.

Warnings and precautions

Talk to your doctor or pharmacist before taking Ketoconazole HRA.

Liver disease
Speak with your doctor if you have a history of liver disease. You should know that your liver enzyme tests will be regularly monitored before starting the treatment, once weekly during the first month after Ketoconazole HRA initiation and then monthly for 6 months due to the risk of serious hepatic toxicity. They will be checked again after that in case your doctor increases your daily ketoconazole dose. **You should stop your 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.**

Specific dosing regimen
If you take concomitant glucocorticoid replacement therapy with your Ketoconazole HRA treatment, your doctor should inform you how to adapt your glucocorticoid replacement therapy dose if you are under stress or have surgery or an infection. In addition, you should receive an emergency card and should be equipped with an emergency glucocorticoid set.

Adrenal function
Your adrenal function will be monitored at regular intervals as this is the standard care in the follow-up of Cushing's syndrome therapy and since adrenal insuficiency 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.

Heart disease
Ketoconazole HRA can change how your heart beats – this can be serious. **Contact your doctor immediately, if you get palpitations or an irregular heartbeat during treatment.**

Coexisting inflammatory/autoimmune disorders
Tell your doctor if you suffer from an autoimmune disorder, you will be closely supervised.

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

Other medicinal products and Ketoconazole HRA
Tell your doctor or phamacist if you are taking, have recently taken or might take any other medicines. **There are some medicines that must not be taken with Ketoconazole HRA (see section 2).** Ask your doctor or pharmacist for more information if you are taking Ketoconazole HRA with other medicines.

Medicines that can interact with Ketoconazole HRA include:
- pasireotide, another drug used to treat a subset of the Cushing's syndrome because it can lead to severe side effects in patients suffering from cardiac disorders
- medicines taken by mouth that prevent blood clots from forming: rivaroxaban, apixaban, edoxaban, cilostazol, warfarin and others coumarin like
- HIV medicines such as maraviroc, indinavir, nevirapine, ritonavir
- certain medicines used for cancer 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, isoniazide, clarithromycin, isavuconazole
- certain antidiabetics: repaglinide, saxagliptin, tolbutamide
- certain medicines used for mental disorders: buspirone, aripipazole, haloperidol, reboxetine, risperidone
- certain heart medicines – verapamil, digoxin, nadolol, aliskiren
- certain anticonvulsivants: carbamazepine, phenitoin
- certain glucocorticoids – such as budesonide, fluticasone, dexamethasone, methylprednisolone, ciclesonide
- certain stong painkillers (narcotics) – such as alfentanyl, fentanyl, buprenorphine (injection and sublingual), oxycodone
- certain medicines used for nausea and vomiting: domperidone, aprepitant
- naloxegol (medicine for treatment of constipation specifically caused by strong pain medicines)
- solifenacin, fesoterodine in patients with renal impairment
- others: sildenafil, , tolterodine, mitotane, praziquantel, eletriptan, , salmeterol, bosentan, midazolam (by injection), tadalafil, vardenafil, temsirolimus, cinalcacet, tacrolimus, ebastine, ciclosporine, colchicine

You should not take antacids (eg aluminium hydroxide) or other medicines for acid indigestion for at least 2 hours after the intake of Ketoconazole HRA (see section Warning and Precautions).

<u>Ketoconazole HRA with alcohol</u>
No alcohol should be consumed during treatment with ketoconazole.

Pregnancy, breast-feeding and fertility
Do not take this medicinal product during pregnancy. If you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Do not breastfeed your baby if you are taking Ketoconazole HRA.

Driving and using machines
Dizziness or somnolence have been reported during treatement with Ketoconazole HRA. Do not drive or operate machines if you experience these symptoms.

Ketoconazole HRA contains lactose
If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Ketoconazole HRA

Initiation and follow up of the treatment must be supervised by specialists in endocrinology.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will test your blood before you start the treatment and regularly during the treatment to detect any possible abnormalities and also to measure the levels of cortisol. The dose will be adapted to your condition with the aim to restore normal cortisol levels.

The recommended initial dose is usually 600 mg per day taken orally (3 tablets per day in 3 divided times). A daily dose from 400 mg per day (2 tablets) to 1,200 mg per day (6 tablets) taken orally in 2 to 3 divided doses may be required to restore your normal cortisol levels.

If you take more Ketoconazole HRA than you should
If you have taken more than the prescribed dose of Ketoconazole HRA, you must contact your doctor immediately.

If you forget to take Ketoconazole HRA
Do not take a double dose to make up for a forgotten dose. If you forget to take one dose, take this dose as soon as you remember. Then go on with regular schedule as prescribed. Do not change the prescribed dose yourself.

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

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

4. Possible side effects

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

Some side effects may be serious. Liver problems can rarely happen (may affect up to 1 in 1,000 people).
Stop taking Ketoconazole HRA and tell your doctor straight away if you experience any of the following:
- long-lasting severe headache or blurred vision
- severe lack of appetite (anorexia)
- weight loss
- nausea or vomiting
- unusual tiredness or fever
- stomach pain
- muscle weakness
- yellowing of the skin or 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) to below the normal range, but your doctor will correct this using appropriate hormone medicines 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 (may affect more than 1 in 10 people)**:**

- An elevated levels of liver enzymes in your blood

Common side effects (may affect up to 1 in 10 people)**:**

- Nausea
- Abdominal pain
- Vomiting
- Diarrhoea
- Skin reactions (pruritus, rash)

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Allergic reactions which can, rarely, be serious
- Change in laboratory markers
- Platelet count decreased
- Headache
- Dizziness
- Sleepiness
- Skin reactions (urticaria)
- Hair loss
- Fatigue

Very rare side effects (may affect up to 1 in 10,000 people)**:**

- Pyrexia (fever)

Side effects with frequency not known (frequency cannot be estimated from the available data)**:**

- Insomnia
- Nervousness
- Intolerance to alcohol
- Loss of appetite or increased appetite
- Headache
- Sensation of tingling or pricking
- Aversion to light
- Bleeding from the nose
- Dyspepsia (impaired digestion)
- Flatulence
- Tongue discoloration
- Dry mouth
- Distortion of the sense of taste
- Skin redness, drying, itching
- Photosensitivity (increase in the reaction to sunlight: redness, itching rash)
- Myalgia (muscle pain)
- Arthralgia (joint pain)
- Menstrual disorders
- Azoospermia (no sperm count)
- Erectile dysfunction
- Gynaecomastia (enlargement in breast tissues in male)
- Oedema peripheral (dropsy in extremities)
- Malaise
- Hot flush
- Transient decrease of testosterone, a male hormone (androgen) made by the body, mostly produced in the testes

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ketoconazole HRA

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.
- This medicine 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.

6. Contents of the pack and other information

What Ketoconazole HRA contains
- The active substance is ketoconazole. Each tablet contains 200 milligram ketoconazole
- The other ingredients are maize starch, lactose monohydrate (see section 2), povidone, microcrystalline cellulose, silica colloidal, magnesium stearate

What Ketoconazole HRA looks like and contents of the pack
Ketoconazole HRA is available in packs containing 60 tablets.

Marketing Authorisation Holder
HRA Pharma Rare Diseases
200 avenue de Paris
92320 CHATILLON
France

Manufacturer
Centre Spécialités Pharmaceutiques
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France

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99-300 Kutno
Poland

This leaflet was last revised in November 2019

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.