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EPAR summary for the public

Ketoconazole HRA

ketoconazole

This is a summary of the European public assessment report (EPAR) for Ketoconazole HRA. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Ketoconazole HRA.

For practical information about using Ketoconazole HRA, patients should read the package leaflet or contact their doctor or pharmacist.

What is Ketoconazole HRA and what is it used for?

Ketoconazole HRA is a medicine used to treat adults and children above the age of 12 years with Cushing's syndrome. Cushing's syndrome is a disease characterised by an excess production of the hormone cortisol by the adrenal glands, two glands situated above the kidneys.

The active substance in Ketoconazole HRA is ketoconazole. Because the number of patients with Cushing's syndrome is low, the disease is considered 'rare', and Ketoconazole HRA was designated an 'orphan medicine' (a medicine used in rare diseases) on 23 April 2012.

How is Ketoconazole HRA used?

Ketoconazole HRA is available as tablets (200 mg). It can only be obtained with a prescription and treatment must be started and supervised by a doctor experienced in treating patients with Cushing syndrome who has access to appropriate facilities to assess the patient's response.

The usual treatment dose is between 400 mg and 1,200 mg per day taken in two or three divided doses. The dose is adjusted according to the levels of cortisol in the body, which is measured by regular checks of the urine or blood.

The patient's liver function should be checked with blood tests before treatment is started and regularly for the following 6 months. The patient's liver function should also be checked weekly for one

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month when the dose is increased. If liver enzyme levels in the blood increase beyond three times the normal maximum (a sign of possible liver problems) or in case of symptoms such as lack of appetite, nausea, vomiting, fatigue, jaundice, abdominal pain (stomach ache) or dark urine that may suggest a liver problem, treatment must be stopped.

For further information, see the package leaflet.

How does Ketoconazole HRA work?

The active substance in Ketoconazole HRA, ketoconazole, is a well known substance that has been authorised for several decades for the treatment of fungal infections. Ketoconazole can still be found in topical medicines (medicines applied to the skin) to treat fungal infections. However, oral formulations (used by mouth) for the treatment of fungal infections were suspended in July 2013 because of the risk of liver injury.[1]

Ketoconazole blocks the activity of a group of enzymes in the adrenal glands involved in the production of cortisol, such as 17 alpha-hydroxylase or 11β-hydroxylase. Blocking cortisol production will help to reduce cortisol levels in the body, thereby relieving the symptoms of the disease. Ketoconazole can also block the production of other hormones produced by the adrenal gland which are often raised in Cushing's syndrome.

What benefits of Ketoconazole HRA have been shown in studies?

Because ketoconazole is a well-known substance, and its use in Cushing's syndrome is well established, the applicant presented data from the published literature on more than 800 patients with Cushing's syndrome who were treated with ketoconazole either alone or in combination with other treatments. The average dose used was 600 to 800 mg per day. The main measure of effectiveness in these literature studies was the level of cortisol in the urine. Ketoconazole treatment was shown to normalise urine cortisol levels in 43 to 80% of patients.

What are the risks associated with Ketoconazole HRA?

The most common side effects with Ketoconazole HRA are adrenal insufficiency (too low a level of the hormones produced by the adrenal gland), nausea (feeling sick), vomiting, abdominal pain (stomach ache), diarrhoea, pruritus (itching), rash and increase in blood levels of liver enzymes. The most serious side effects are liver problems which can be detected early through regular monitoring.

Ketoconazole HRA must not be used in patients with liver disease or whose blood levels of liver enzymes are above a certain level. It must also not be used in pregnant or breastfeeding women or patients who have QTc prolongation (disruption of the electrical activity of the heart). Ketoconazole HRA must also not be used together with certain medicines that may increase the risk of serious side effects.

For the full list of all side effects and restrictions with Ketoconazole HRA, see the package leaflet.

Why is Ketoconazole HRA approved?

The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Ketoconazole HRA's benefits are greater than its risks and recommended that it be approved for use in the EU.

[1] In the context of a referral procedure under Article 31 of Directive 2001/83/EC. More information can be found here.

The CHMP considered that the use of Ketoconazole HRA to treat Cushing's syndrome was well established in medical practice and documented in the scientific literature. In addition the CHMP considered that additional treatment options are needed for this rare disease.

Regarding its safety the CHMP considered that the risk of liver problems can be managed through appropriate measures.

What measures are being taken to ensure the safe and effective use of Ketoconazole HRA?

A risk management plan has been developed to ensure that Ketoconazole HRA is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Ketoconazole HRA, including the appropriate precautions to be followed by healthcare professionals and patients.

Further information can be found in the summary of the risk management plan.

The company that makes Ketoconazole HRA will also provide doctors who will use Ketoconazole HRA with a letter containing information regarding the risks of side effects, particularly of liver injury, and how to use the medicine properly. The company will also set up a registry of patients treated with Ketoconazole HRA in order to monitor the safety and effectiveness of the medicine.

Other information about Ketoconazole HRA

The European Commission granted a marketing authorisation valid throughout the European Union for Ketoconazole HRA on 19 November 2014.

The full EPAR and risk management plan summary for Ketoconazole HRA can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports. For more information about treatment with Ketoconazole HRA, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

The summary of the opinion of the Committee for Orphan Medicinal Products for Ketoconazole HRA can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

This summary was last updated in 11-2014.