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Ketoconazole HRA™: Information about the risk of hepatotoxicity

Dear Healthcare Professional,

Laboratoire HRA Pharma, in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA), would like to inform you about important safety information in relation to Ketoconazole HRA, authorised for the treatment of endogenous Cushing's syndrome in adults and adolescents above 12 years.

Summary

- **Ketoconazole HRA treatment should be initiated and supervised by physicians experienced in the treatment of Cushing's syndrome and having the appropriate facilities for monitoring of biochemical responses since the dosage must be adjusted to meet the patient's therapeutic need, based on the normalisation of cortisol levels.**
- **Ketoconazole HRA is contraindicated in patients with acute or chronic liver disease and/or if pre-treatment liver enzymes levels are above 2 times the upper limit of normal.**
- **To minimise the risk of severe liver injury, monitoring of liver function tests is mandatory in all patients receiving Ketoconazole HRA before initiation and periodically thereafter as recommended in the Product Information:**
 - **Before starting the treatment:**
 - measure liver enzymes (ASAT, ALAT, gammaGT and alkaline phosphatase) and bilirubin
 - inform the patients about the risk of hepatotoxicity, including to stop the treatment and to contact their doctor immediately if they feel unwell or in the event of symptoms such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. If these occur, treatment should be stopped immediately and liver function tests should be performed.

○ **During the treatment:**

- close clinical follow-up should be undertaken
- measurement of liver enzymes (ASAT, ALAT, gamma GT and alkaline phosphatase) and bilirubin, should be performed at frequent intervals:
 - weekly for one month after initiation of the treatment
 - then monthly for 6 months
 - weekly for one month whenever the dose is increased.

- **In the case of an increase in liver enzymes of less than 3 times the upper limit of normal, more frequent monitoring of liver function tests should be performed and the daily dose should be decreased by at least 200 mg.**
- **In the case of an increase in liver enzymes equal to or greater than 3 times the upper limit of normal, Ketoconazole HRA should be stopped immediately and should not be reintroduced due to the risk of serious hepatic toxicity.**

● **Ketoconazole HRA should be discontinued without delay if clinical symptoms of hepatitis develop.**

● **In the case of long term treatment (more than 6 months):**

Although hepatotoxicity is usually observed at treatment initiation and within the first six months of treatment, monitoring of liver enzymes should be continued as clinically appropriate. As a precautionary measure, should a dose increase be required after the first six months of treatment, monitoring of liver enzymes should be performed on a weekly basis for one month.

Further information on the hepatotoxic risk

Ketoconazole HRA is authorised for the treatment of endogenous Cushing's syndrome in adults and adolescents. The recommended dosage at initiation is 400-600 mg/day taken orally in two or three divided doses and this dose can be increased rapidly to 800-1200 mg/day in two or three divided doses.

Ketoconazole oral tablets for an anti-fungal indication were previously subject to a referral procedure in Europe due to public health concerns regarding the risk of hepatotoxicity. In 2013, the marketing authorizations of oral ketoconazole-containing medicines in this indication were suspended. The recommended daily dose was 200 mg/day.

The onset of hepatotoxicity with ketoconazole usually occurs between 1 and 6 months after initiation of treatment but has also been reported earlier than 1 month (including cases occurring in only a few days) after initiation of treatment or in the case of a dose increase. Most of the clinical experience comes from the use of ketoconazole as an anti-fungal therapy. The mechanism of liver damage caused by ketoconazole is not fully understood. Besides the cases of acute hepatitis the most frequent observation is the occurrence of mild asymptomatic liver enzymes elevations.

Further information

More information is provided in the Product Information for Ketoconazole HRA 200 mg tablets. Should you have further medical questions, you can contact HRA Pharma local representative, HRA Pharma UK & Ireland Ltd, Tel: 1800 812 984 or email: med.info.ie@hra-pharma.com.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via HRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.

Website: www.hpra.ie ; E-mail: medsafety@hpra.ie.

Any suspected adverse reactions observed during use of Ketoconazole HRA should also be reported to HRA Pharma UK & Ireland Ltd, Tel: 1800 812 984 or email: med.info.ie@hra-pharma.com.

Yours faithfully,



Emilie Prevosto

European Qualified Person for Pharmacovigilance