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DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

▼Ketoconazole HRA™: Information about the risk of hepatotoxicity

Dear Healthcare professional,

In agreement with the European Medicines Agency (EMA) and the Medicines Authority of Malta, Laboratoire HRA Pharma 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

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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 during one month whenever the dose was 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 any delay if clinical symptoms of hepatitis develop.**
- **In 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 done under medical criteria. As a precautionary measure, in case of a dose increase after the first six months of treatment, monitoring of liver enzymes should be repeated on a weekly basis for one month.

Further information on the hepatotoxic risk

Ketoconazole HRA™ is authorised in 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 800-1 200 mg/ day in two or three divided doses.

Ketoconazole oral tablet in the anti-fungal indication was previously subject to a referral procedure in Europe due to public health concerns on the hepatotoxicity risk. In 2013, the

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marketing authorizations of oral ketoconazole-containing medicines in the antifungal indication were suspended where 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 few days) after initiation of treatment or in 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 secondary to ketoconazole is not fully clear. 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 of Ketoconazole HRA™ 200mg tablets. In case of any medical question, you can contact by email the medical department of medinfo-od@hra-pharma.com.

Call for reporting

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Please report any suspected adverse reactions to any medicine to the Medicines Authority of Malta through ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

Yours faithfully,

Delphine Cossard

Pharmacovigilance Manager