25 September 2014
EMA/CHMP/568353/2014
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Ketoconazole HRA

ketoconazole

On 25 September 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Ketoconazole HRA, 200mg tablets intended for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.

Ketoconazole HRA was designated as an orphan medicinal product on 23 April 2012. The applicant for this medicinal product is Laboratoire HRA Pharma. They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The active substance of Ketoconazole HRA is ketoconazole a potent inhibitor of cortisol synthesis and aldosterone synthesis from its ability to inhibit several cytochrome P450 enzymes in the adrenal glands. Ketoconazole is also a potent inhibitor of androgens synthesis. Apart from adrenal blocking effect, ketoconazole may also have direct effects on corticotropic tumour cells in patients with Cushing's disease.

The benefits with Ketoconazole HRA are its ability to allow a long-term control of hypercortisolism. The biochemical and hormonal improvements observed (measure of decreases or normalization of urinary free cortisol levels) are usually associated with clinical improvements in Cushing's Syndrome symptoms. The clinical experience suggests that ketoconazole may be a valuable drug for the short-term or the long term medical management of the patients with Cushing's Syndrome, whenever a medical therapy is indicated.

The most common side effects are adrenal insufficiency, nausea, vomiting, abdominal pain, diarrhoea, pruritus, rash and increased hepatic enzymes. The most significant adverse reaction is hepatotoxicity requiring monitoring of liver function prior and during treatment. Adrenal insufficiency and ECG monitoring are also required. Furthermore, a careful approach is needed with regards to potential drug-drug interactions due to its metabolism.

[1] Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion.

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A pharmacovigilance plan for Ketoconazole HRA will be implemented as part of the marketing authorisation.

The approved indication is: "Ketoconazole HRA is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years".

It is proposed that Ketoconazole HRA should be initiated and supervised by physicians experienced in endocrinology or internal medicine 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.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-to-risk balance for Ketoconazole HRA and therefore recommends the granting of the marketing authorisation.