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Drug Shortage Recommendations

To: The scientific committee of Dutch Society of Endocrinology "Nederlandse Vereniging voor Endocrinologie"

Dear Madam or Sir,

HRA Pharma regrets to inform you that we are facing a temporary supply interruption of Metopirone® (Metyrapone) used for the treatment of Endogenous Cushing's syndrome. The reason for this interruption is transient manufacturing difficulties.

Continued effective and safe treatment for patients is the first priority of HRA Pharma. Therefore, we have worked closely with two medical & scientific experts in Cushing's syndrome, Prof. Antoine Tabarin (Bordeaux, France) and Prof. John Newell-Price (Sheffield, UK), to establish recommendations on alternatives for patients currently taking Metopirone® (Metyrapone). **These recommendations are scientific advice only & are to be reviewed and adapted as per the local guidelines and physicians' experience**. **This letter mustn't be diffused externally.**

In order to minimize the disruption of the patient's care, Pr. Antoine Tabarin (Bordeaux, France) & Pr. John Newell-Price (Sheffield, UK) recommend to consider at first instance switching to a drug of the same therapeutic class (Steroidogenesis inhibition) such as Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) in the following cases:

- Patients on stable long-term treatment or with a need of prolonged treatment with Metopirone® (Metyrapone).

- Patients with no previous history of intolerance with Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) (in this instance consider that a mild increase (< 3xULN) in liver enzymes is common during the first weeks following Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) initiation(1) and does not necessarily indicate a major and definitive intolerance).
- Patients with Cushing's disease who have received pituitary radiation and require steroidogenesis inhibitors.
- Patients with Cushing's disease in those centres that routinely treat with steroidogenesis inhibitors prior to pituitary surgery.
- Patients with ectopic ACTH causing Cushing's syndrome for whom bilateral-adrenalectomy is not indicated.

Important information:

- Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years. It is effective for long-term control of hypercortisolism and requires stomach acidity for dissolution and absorption.
- Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) is contraindicated in pregnant and breastfeeding women.
- Kindly note that there is no dose equivalence between Metopirone® (Metyrapone) & Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole). Experts suggest initiation of treatment in most patients with an average dosage of 600 mg/day in divided doses of Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole), with individualised titration depending on biochemical monitoring and clinical tolerance.
- Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) can be titrated up or down by 200 mg depending on the patient profile. To be effective dose titration to a maximum daily dose of 1200 mg (divided into two or three equal doses) per day may be needed. Conversely, in the case of adrenal insufficiency, the dose of Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) should be reduced, or temporarily discontinued and if necessary corticosteroid substitution should be initiated. Titration must be assessed by urinary free cortisol and/or by use of plasma/serum cortisol levels measurement based on the standard local protocol. Please find more details in the local drug's SmPC (2) (section: 4.2).

- Monitor liver, adrenal and cardiac function during Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole) treatment in order to prevent hepatotoxicity, adrenal insufficiency or prolongation in QTc interval. Please refer carefully to the local drug's SmPC (section 4.2) for full details of necessary monitoring.
- Monitor drug interactions with Ketoconazole HRA® 200 mg, tablets (INN: ketoconazole). Caution should be considered with drugs that have narrow therapeutic windows and are substrates of the CYP3A4 enzymes, P-gp, and BRCP transporters. Please refer carefully to the local drug's SmPC (sections 4.4 & 4.5) for full details of drug interactions.

Other medical therapeutic options belonging to another therapeutic class, are also available for Cushing's syndrome, and their suitability should be assessed on a case-by-case basis. Please refer to international guidelines [3].

Please don't hesitate to review and amend these recommendations based on your practice, experience and medication availability in your country.

HRA strongly encourage you to consider these recommendation with the experts of Cushing's syndrome who are members of your society to adapt these recommendations to the current practices in your country. HRA pharma and the experts above are at your disposable for future interactions.

HRA Pharma is monitoring this shortage very closely in order to ensure that all patients receive the best quality care and treatment.

Should you have any questions or concerns about the information mentioned above please contact us on medinfo-od@hra-pharma.com.

We will inform you when Metopirone® (Metyrapone) is again available for your patients.

Ketoconazole® HRA's SmPC is attached to this letter in order to provide you with the complete information needed.

Thank you for your patience and understanding.

References:

(1) Young J, Bertherat J, Vantyghem MC, Chabre O, Senoussi S, Chadarevian R, Castinetti et al. Hepatic safety of ketoconazole in Cushing's syndrome: results of a Compassionate Use Programme in France. Eur. J. Endocrinol, 2018 May;178(5):447-458.

(2) SmPC Ketoconazole.

(3) Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, August 2015, 100 (8):2807–2831.

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