HRA Pharma Deutschland GmbH
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20. Februar 2019

Notice of Temporary Out Of Stock

Dear Health Care Professional,

HRA Pharma would like to inform you of a temporary shortage situation for the supply of the product below. The reason for this temporary interruption to supply is due to manufacturing difficulties.

Product Name affected	License Number	Unavailability Date	Resupply Date
Metopiron® (INN: Metyrapon) 250 mg Weichkapseln	91422.00.00	Februar 2019	Mai 2019

HRA Pharma is working diligently to resolve the supply shortage and resumption of the supply as soon as possible. The quality, safety, and efficacy of Metopiron® already on the market are not affected by this situation.

Additional Information – Alternative medicinal products:

Continued effective and safe treatment for patients is the first priority of HRA. Therefore, we have worked closely with medical & scientific experts composed of Prof. Antoine Tabarin (France) and Prof. John Newell-Price (UK) to establish a backup plan for patients currently taking Metopiron®. We believe the experts' recommendations will enable patient needs to continue to be met.

During this situation of shortage, the following therapeutic alternative using a drug of the same therapeutic class (Steroidogenesis inhibition) can be followed to minimise disruption to patient care.

Ketoconazole HRA® 200 mg Tabletten (INN: ketoconazole) is also a steroidogenesis inhibitor registered in Europe (EU/1/14/965/001) for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years. Please refer carefully to the medicinal product's Summary of Product Characteristics (SmPC)[1] for warning and precautions for use (especially the contraindication in pregnant and breastfeeding women, the monitoring of liver function and adrenal function and the interactions with other drugs).

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Our medical & scientific experts have advised HRA Pharma that many patients without history of adverse events with ketoconazole should, depending on their profile, be able to switch to ketoconazole for continued safe and effective therapy of endogenous Cushing's syndrome.

Oral ketoconazole treatment is initiated at a daily dose of 400 mg to 600 mg divided into 2 or 3 doses that can be titrated up or down by 200 mg depending on the patient's needs. In considering the switch from Metopiron® to Ketoconazole HRA®, our experts believe that an initial dose of 600 mg is most likely appropriate starting dose for most patients, with individual adjustment thereafter. To reach the effective dose, titration should be performed with a maximum licensed dose of 1200 mg divided into two or three equal doses per day. Conversely, in case of adrenal insufficiency, ketoconazole dosage should be reduced, or temporarily discontinued and if necessary corticosteroid substitution should be initiated. Titration must be assessed by urinary free cortisol and/or serum or plasma cortisol levels measurement. It should be highlighted that low pH stomach acid is usually needed for the proper absorption of ketoconazole.

During ketoconazole treatment, owing to the risk of hepatotoxicity, adrenal insufficiency or prolongation in QTc interval, monitoring of liver, adrenal and cardiac functions is mandatory. Please refer carefully to the drug's SmPC for full details of necessary monitoring.

Ketoconazole is mainly metabolised by the cytochrome P450 3A4 isoenzyme system. Consequently, caution should be exercised and close monitoring is mandatory when concomitantly administering ketoconazole with drugs that have narrow therapeutic windows and are substrates of the CYP3A4 enzymes and P-gp and BRCP transporters. Please find the product details in the SmPC attached to this letter which also details other warnings and precautions, as well as contraindications.

Other medical therapeutic options are also available for the specific situation of Cushing's syndrome, and their suitability should be assessed on a case-by-case basis. Please refer to the international guidelines[2]. Other drugs may be used according to the local recommendations and local market regulations.

HRA Pharma is monitoring this shortage very closely and wishes to ensure that all patients will receive the best quality care and treatment. Should you have any questions or concerns about ketoconazole therapy implementation, please contact us on the platform medinfo-od@hra-pharma.com. We will inform you when Metopiron® is again available for your patients.

You can find the link of Ketoconazole® HRA's SmPC below under "Reference" in order to provide you with the complete information needed.

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Thank you for your patience and understanding.

Ronja Loy
Responsible Person

Vincent Montauban
Person in charge of Medical information

Reference:

(1) SmPC Ketoconazole
https://www.ema.europa.eu/documents/product-information/ketoconazole-hra-epar-product-information_de.pdf

(2) 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.