Product Name	Metycor® 250 mg, capsules soft
Active substance	metyrapone
Indication and conditions of use	Metyrapone is indicated for the management of patients with endogenous Cushing's syndrome. **Posology and method of administration:** ***Adults*** For the management of Cushing's syndrome, the initial dose of metyrapone may vary from 250 to 1,000 mg/day depending on the severity of hypercortisolism and the cause of Cushing's syndrome. Metyrapone may be initiated at doses of 750 mg/day. For patients with severe Cushing's syndrome initiation doses may be higher, up to 1500 mg/day. Lower starting doses may be used in cases of mild Cushing's disease or adrenal adenoma or hyperplasia. The dosage of metyrapone should be adjusted on an individual basis to meet patient's requirements and depending on tolerability. The usual maintenance dose varies between 500 and 6,000 mg/day. The dose should be given in three or four divided doses. The daily dose should be adjusted after a few days with the aim of lowering the mean plasma/serum cortisol levels and/or the 24 hour urinary free-cortisol levels to a normal target value or until the maximal tolerated dose of metyrapone is reached. Mean serum/plasma cortisol levels may be calculated from the average of 5 to 6 plasma/serum samples obtained throughout a day or from cortisol levels obtained just before the morning dose. Once weekly monitoring of plasma/serum cortisol levels and/or a 24-hour free urinary cortisol levels is necessary to allow further dose adjustments if needed. The dose-adjustment period is usually 1 to 4 weeks. When cortisol levels are close to the optimal levels, longer periods (generally once a month or every 2 months) are sufficient for the monitoring. A physiological corticosteroid replacement therapy may be added to a complete cortisol blockade by metyrapone (block-and-replace regimen). This should be started when the serum or urine cortisol is in the normal range and the metyrapone doses are increased to achieve complete suppression of cortisol secretion. In case of rapid dose-escalation or for patients with cyclic Cushing's syndrome, a physiological corticosteroid replacement therapy may be added. ***Elderly populations*** Dosage as for adults. There is limited data available on the use of metyrapone in elderly (≥ 65 years old). Clinical evidence indicates that no special dosage recommendations are required in all indications.

	Method of administration The capsules should be taken with milk or after a meal to minimise nausea and vomiting which can lead to impaired absorption.

Conditions, delays and further rules for participation of patients	Eligibility criteria: Inclusion/Exclusion criteria As mandatory inclusion criteria: o Patients included in the phase III/IV clinical (EudraCT number 2014-000162-22) with metyrapone who have completed the study extension period within the two preceding months and whose physician considers that continuation of the treatment may provide clinical benefit o Patients with normalized mean UFC (mUFC) levels obtained at week 36 (mUFC ≤ ULN) or patients who have mUFC levels close to the target but not exceeding 2-fold ULN (mUFC < 2-fold ULN) at week 36 of the phase III/IV clinical trial (EudraCT reference 2014-000162-22) o Patients showing acceptable tolerability of MTP treatment during the initial 36-week period of the phase III/IV clinical trial (EudraCT reference 2014-000162-22). o Patients should have been clearly and completely informed by the requesting physician and written consent must be provided prior the start of the treatment. o The patient is not eligible for a clinical trial running with metyrapone and/or a clinical trial running in the envisaged indication of this program. o The patient cannot be satisfactorily treated with the approved and commercially available alternative treatments, in accordance with clinical guidelines, because of efficacy and/or safety issues. o The patient should fulfill the recommendations included in the SmPC (provided in Appendix 5 of this protocol. Exclusion criterion: o Patients with mUFC levels ≥ 2-fold ULN at week 36 of the phase III/IV clinical trial (EudraCT reference 2014-000162-22) Process to include a patient in the medical need program : After truly and voluntary written consent from the patient, the treating physician sends a written request (PDF, letter of fax) to the responsible physician of the program. The request must include : o A copy of the ID card of the patient and his social security number if applicable, o A motivation to enroll the patient within this program, o Treating physician declaration form signed by the treating physician and returned to the responsible physician and Laboratoire HRA Pharma. Within this form the treating physician declares that he/she is personally responsible for the use of a medicinal product that is authorised in Belgium for which the sought indication has been obtained but the product is not yet commercially available in Belgium. The treating physician should include a description of the disease in this form and declares that the disease for which the medicinal product is requested is a chronic disease or severely affects patient's health or is life-threatening and cannot be satisfactorily treated by a medicinal product currently marketed and approved for the treatment of the sought indication, o Signed informed consent form

	Patient must accept participation in the Medical Need Program and provide a written informed consent. o Metyrapone 250 mg capsule soft supply request form. Data received by HRA Pharma will be blinded. Indeed, the responsible physician receives non-blinded data (including ID card, social security number when applicable, treating physician declaration form, Informed Consent Form (ICF) …). The responsible physician will anonymize the data (ICF will also be anonymized by hiding any private data such as name of the patient) so that HRA Pharma will only receive the patient study number and his/her birthdate. Nominative data will be exclusively kept by the responsible physician and not transmitted to the responsible of the program ie Laboratoire HRA Pharma. The responsible physician will assess the request within 3 days and gives his advice regarding the admissibility of the patient taking into consideration the possibility to include the patient in an ongoing clinical trial in Belgium. He provides his reasoned advice to the responsible of the program. In case of positive advice, the Laboratoire HRA Pharma will make available the medicinal product to the treating physician within 5 days.
Duration of the program	This program will start as soon as the Medical Need Program is authorized by the authorities. Metyrapone 250 mg capsules soft will be provided free of charge by Laboratoire HRA Pharma on an individual patient basis following the criteria listed in this program until the product will be commercially available in Belgium in the envisaged indication or until, in the clinical judgement of the treating physician, the patient is no longer benefiting from continuation of the treatment, whichever is sooner.
Conditions of distribution	After inclusion of a patient in the MNP, metyrapone 250 mg capsules soft is delivered at the hospital pharmacy of the treating physician.
Responsible of the program	**Responsible physician of the program** : Dr.Natacha Driessens, MD, PhD Service d'endocrinologie - Hôpital Erasme Route de Lennik, 808 1070 Bruxelles Phone: +32 2/555.34.07 Fax: +32 2/555.67.08 Email: natacha.driessens@erasme.ulb.ac.be **Responsible of the program** : Laboratoire HRA Pharma 15, rue Béranger 75003 Paris + 33 1 40 33 11 30 ***Contact person for the patients in the company :*** Amélie Jaspart Clinical trial coordinator / Clinical Quality Officer Laboratoire HRA Pharma 15, rue Béranger 75003 Paris

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amelie.jaspart@hra-pharma.com</td></tr>
<tr><td>Modalities for the disposal</td><td>Any unused medication needs to be returned to Laboratoire HRA Pharma or destroyed in an appropriate facility as soon as possible after the patient’s discontinuation from the Medical Need Program. The medication delivered for an individual patient request in the context of the Medical Need Program can only be used for that particular patient.</td></tr>
<tr><td>The information for registration of suspected unexpected serious adverse reactions</td><td>Safety data are derived from spontaneous reports and published literature. Adverse drug reactions are listed according to system organ classes and preferred terms in MedDRA using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data).
<table>
<tr><th>Frequency</th><th>SOC / Preferred Term</th></tr>
<tr><td colspan="2">Blood and lymphatic system disorders</td></tr>
<tr><td>Not known:</td><td>Bone marrow failure</td></tr>
<tr><td colspan="2">Endocrine disorders</td></tr>
<tr><td>Rare:</td><td>Adrenal insufficiency</td></tr>
<tr><td colspan="2">Nervous system disorders</td></tr>
<tr><td>Common:</td><td>Dizziness, sedation, headache</td></tr>
<tr><td colspan="2">Vascular disorders</td></tr>
<tr><td>Common:</td><td>Hypotension</td></tr>
<tr><td>Not known:</td><td>Hypertension</td></tr>
<tr><td colspan="2">Gastrointestinal disorders</td></tr>
<tr><td>Common:</td><td>Nausea, vomiting</td></tr>
<tr><td>Rare:</td><td>Abdominal pain</td></tr>
<tr><td colspan="2">Skin and subcutaneous tissue disorders</td></tr>
<tr><td>Rare:</td><td>Hirsutism, allergic dermatitis</td></tr>
<tr><td>Not known:</td><td>Alopecia</td></tr>
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