SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT*

Metopirone 250mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Metopirone capsule contains 250 mg metyrapone.

Excipients with known effect
Each capsule contains 0.71 mg of sodium ethyl parahydroxybenzoate and 0.35 mg sodium propyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

White to yellowish-white, oblong, opaque, soft gelatin capsule imprinted in red ink with “HRA” on one side and having faintly yellowish viscous to jelly-like contents.
Capsule size: length 18.5 mm, diameter 7.5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a diagnostic test for ACTH insufficiency and in the differential diagnosis of ACTH-dependent Cushing’s syndrome.

For the management of patients with endogenous Cushing’s syndrome.

4.2 Posology and method of administration

Posology

Diagnostic Applications

(i) Short single-dose test – diagnosis of ACTH insufficiency

This can be performed on an ambulatory basis. In this test, plasma 11- desoxycortisol and/or ACTH levels are determined after a single dose of Metopirone. The patient is given 30 mg/kg (maximum 3 g Metopirone) at midnight with yoghurt or milk to minimise nausea and vomiting.

Paediatric population
The same dose as in adults is recommended in children.

The blood sample for the assay is taken early in the morning (7:30 – 8:00 hours). The plasma should be frozen as soon as possible. The patient is then given a prophylactic dose of 50 mg cortisone acetate.

Evaluation:

Normal values will depend on the method used to determine ACTH and 11-desoxycortisol levels. An intact ACTH reserve is generally indicated by an increase in plasma ACTH to at least 44 pmol/L (200 ng/L) or by an increase in 11-desoxycortisol to over 0.2 micromol/L (70 microg/L). Patients with suspected adrenocortical insufficiency should be hospitalised overnight as a precautionary measure.

(ii) Multiple-dose test – diagnosis of ACTH insufficiency and differential diagnosis of adrenocortical hyperfunction in Cushing's syndrome.

The patient must be hospitalised. In this test, urinary steroid levels are measured. The first day, baseline values are determined for the 24 hours preceding the test. The second day, 500-750 mg Metopirone are administered every 4 hours for 24 hours, giving a total dose of 3.0-4.5 g. The effect is evaluated in two consecutive 24-hour urinary samples. The maximum effect of Metopirone on urinary steroid values should be reached within the next 24 hours.

Paediatric population
The paediatric dosage recommendation is based on limited data. In children the dosage should be 15 mg/kg body weight, with a minimum dose of 250 mg every 4 hours for 6 doses.

It is recommended that patients take the capsules with milk or after meals to minimise nausea and vomiting.

Evaluation:

ACTH deficiency:
If the anterior pituitary is functioning normally, Metopirone brings about a marked increase in 17-hydroxycorticosteroids (17–OHCS) or 17 ketogenic steroids (17–KGS) in the urine (to at least twice baseline levels). Lack of response indicates secondary adrenocortical insufficiency.

Cushing's syndrome:
An excessive increase in 17–OHCS or 17–KGS in the urine after administration of Metopirone indicates over-production of ACTH which has led to adrenocortical hyperplasia (Cushing's syndrome). Such an increase can be taken as an indication that there is no adrenocortical tumour producing cortisol autonomously.

Therapeutic Use

Adults
For the management of Cushing's syndrome, the initial dose of metyrapone may vary from 250 to 1500 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 moderate Cushing's syndrome. 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.

Special populations

Paediatric population:
The paediatric dosage recommendation is based on limited data. Case reports showed that there is no specific dosage recommendation for paediatric use in the treatment of Cushing's syndrome. The dose should be adjusted on an individual basis as a function of cortisol levels and tolerability.

Elderly population:
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.

4.3 Contraindications

- Manifest primary adrenocortical insufficiency.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diagnostic applications

The metyrapone diagnostic test should be restricted to referral hospital centers.

Patients with reduced adrenal secretory capacity and serious hypopituitarism
The ability of the adrenal cortex to respond to exogenous ACTH should be demonstrated before Metopirone is employed as a test, because Metopirone may induce acute adrenal insufficiency in patients with reduced adrenal secretory capacity as well as in patients with global pituitary insufficiency. The test should be performed in hospital with close monitoring in case of suspected adrenocortical insufficiency.

Reduced liver function
Patients with liver cirrhosis often show a delayed response to Metopirone due to liver damagedelaying the plasma elimination half-life of cortisol.

Patients with hypothyroidism or taking drugs affecting the hypothalamo-pituitary adrenal axis
In cases of thyroid hypofunction, urinary steroid levels may rise very slowly, or not at all, in response to Metopirone. Before the Metopirone test is carried out, drugs affecting pituitary or adrenocortical function should be discontinued (see section 4.5). If adrenocortical or anterior pituitary function is more severely compromised than indicated by the results of the test, Metopirone may trigger transient adrenocortical insufficiency. This can be rapidly corrected by giving appropriate doses of corticosteroids.

Therapeutic use

Hypocortisolism
The product should only be used under the supervision of specialists having available the appropriate facilities for monitoring of clinical and biochemical responses. Treatment with Metopirone leads to rapid decrease in circulating levels of cortisol and potentially to hypocortisolism/hypoadrenalism. It is therefore necessary to monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyperkalaemia, hyponatraemia, hypoglycaemia). In the event of documented hypocortisolism, temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of Metopirone therapy may be necessary.

Assay methods
A reliable assay without cross-reactivity with steroids precursors, such as a specific immuno-assay or a liquid chromatography-mass spectrometry (LC-MS/MS) method, to measure plasma/serum and urine cortisol levels is recommended to allow accurate metyrapone dose adjustment.

Patients with severe Cushing's syndrome
Severe Cushing's syndrome is known to increase the risk of opportunistic infections such as Pneumocystis jirovecii pneumonia due to immunosuppression and anti-inflammatory effect of hypercortisolism. Generally, infection must be anticipated in such patients and careful management and appropriate prophylactic treatment is recommended in this population.

Hypertension
Long-term treatment with Metopirone can cause hypertension as the result of excessive secretion of desoxycorticosterone.

Hypokalaemia
Hypokalaemia can occur in patients with Cushing's syndrome and during Metopirone treatment. Potassium levels should be checked before therapy start and monitored periodically during therapy.
Any hypokalaemia prior to Metopirone administration and/or during therapy should be corrected.

QTc prolongation
In a clinical study performed in patients with Cushing's syndrome treated with metyrapone (PROMPT, prospective single-arm, open-label study, 50 patients included in safety data set), three patients had an asymptomatic increase in QTcF interval above 60 ms. No patient had an increase of QTcF interval above 480 ms.
Metyrapone should be used with caution in patients with relevant pre-existing cardiac diseases and/or electrolyte disturbances. If signs of cardiac arrhythmia occur during treatment with Metopirone, monitoring of ECG and electrolytes are recommended.

Breast-feeding
There is insufficient information on the excretion of metyrapone in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Metopirone (see section 4.6).

Excipients
The presence of the excipients sodium ethyl parahydroxybenzoate (E215) and sodium propyl parahydroxybenzoate (E217) can cause allergic reactions, which might be delayed.
This medicine contains less than 1 mmol sodium (23 mg) per capsule. It is essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

The interaction potential of metyrapone is partly unknown and therefore caution is advised when initiating and discontinuing treatment with other medicinal products. If changes to the effect and/or safety profile of metyrapone or the concomitant drug are seen, suitable action should be taken.

Observed interactions

In relation to use as a diagnostic aid: Anticonvulsants (e.g. phenytoin, barbiturates), anti-depressants and neuroleptics (e.g. amitriptyline, chlorpromazine, alprazolam), hormones that affect the hypothalamo-pituitary axis, corticosteroids, antithyroid agents and cyproheptadine may influence the results of the Metopirone test.

If these drugs cannot be withdrawn, the necessity of carrying out the Metopirone test should be reviewed.

Anticipated interactions

Metopirone may potentiate paracetamol (acetaminophen) toxicity in humans.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or a limited amount of data from the use of metyrapone in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Metopirone is not recommended during pregnancy when used as a diagnostic test or for the management of endogenous Cushing's syndrome unless the potential benefit outweighs the risks (in this case, blood pressure should be monitored and hypertension managed appropriately to avoid complications such as pre-eclampsia) and in women of childbearing potential not using contraception.
Transplacental passage of metyrapone has been shown in animals and humans. Therefore, if Metopirone is required during the pregnancy, cortisol and electrolytes levels in neonate should be monitored at birth and the week after or until resolution, to monitor for the potential risk of adrenal insufficiency (rare cases of transient low cortisol have been reported in neonates exposed in utero). Glucocorticoid replacement may be needed.

Breast-feeding
There is insufficient information on the excretion of metyrapone in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Metopirone (see section 4.4).

Fertility
The effect of metyrapone on human fertility has not been investigated in clinical studies. In animals,

metyrapone has been shown to cause adverse effects on spermatogenesis and ovarian follicular development; however no formal fertility studies have been conducted (see section 5.3).

4.7 Effects on ability to drive and use machines

Metopirone has a minor influence on the ability to drive and use machines. Since Metopirone may cause dizziness and sedation, patients should not drive or operate machinery until these effects have passed.

4.8 Undesirable effects

Safety data are derived from spontaneous reports, published literature and PROMPT study (prospective single-arm, open-label study, 50 patients included in safety data set). Adverse drug reactions (Table 1) 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 1 Adverse drug reactions

System Organ Class	Frequency SOC / Preferred Term		
	Very common (≥1/10)	Common (≥1/100, <1/10)	Not known
Blood and lymphatic system disorders			Leukopenia, anaemia, thrombocytopenia
Endocrine disorders	Adrenal insufficiency*		
Metabolism and nutrition disorders	Decreased appetite*	Hypokalaemia	
Nervous system disorders	Headache* Dizziness*	Sedation	
Vascular disorders	Hypertension	Hypotension*	
Gastrointestinal disorders	Nausea* Abdominal pain* Diarrhoea	Vomiting*	
Hepatobiliary disorders			Hepatic enzymes increased
Skin and subcutaneous tissue disorders	Hypersensitivity reactions including rash, pruritus and urticaria	Hirsutism** Acne	Alopecia
Musculoskeletal and connective tissue disorders	Arthralgia	Myalgia	
Infections and Infestations			Pneumocystis jirovecii pneumonia

General disorders and administration site conditions	Asthenic conditions Peripheral oedema		

*Mainly during titration period / dose increase

**Reported cases occurred in the PROMPT study following treatment of 12 to 36 weeks duration

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms: The clinical picture of acute Metopirone poisoning is characterised by gastro– intestinal symptoms and acute adreno-cortical insufficiency.

Laboratory findings: hyponatraemia, hypochloraemia, and hyperkalaemia. In patients under treatment with insulin or oral anti-diabetics, the signs and symptoms of acute poisoning with Metopirone may be aggravated or modified.

Treatment: There is no specific antidote. Immediate treatment is essential in the management of metyrapone overdose, patients should be referred to hospital urgently for immediate medical attention. Treatment with activated charcoal may be considered if the overdose has been taken within 1 hour. In addition to general measures, a large dose of hydrocortisone should be administered at once, together with IV saline and glucose. This should be repeated as necessary in accordance with the patient's clinical condition. For a few days blood pressure and fluid electrolyte balance should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic agent, test for pituitary function, ATC code: V04CD01

Metopirone acts by inhibiting adrenocorticosteroid synthesis. It reduces cortisol and corticosterone production by inhibiting the 11β-hydroxylation reaction in the adrenal cortex. Removal of the strong inhibitory feedback mechanism exerted by cortisol results in an increase in adrenocorticotrophic hormone (ACTH) production by the pituitary. Continued blockade of the enzymatic steps leading to production of cortisol and corticosterone produces a marked increase in adrenocortical secretion of their immediate precursors, 11-desoxycortisol and desoxycorticosterone, which are weak suppressors of ACTH release, and a corresponding increase in plasma levels of these steroids and of their metabolites in the urine. These metabolites can easily be determined by measuring urinary 17-hydroxycorticosteroids (17 OHCS) or 17-ketogenic steroids (17-KGS). Metopirone is used as a diagnostic test on the basis of these properties, with plasma 11-desoxycortisol and urinary 17–OHCS measured as an index of pituitary ACTH responsiveness. Metopirone may also suppress biosynthesis of aldosterone, resulting in mild natriuresis.

5.2 Pharmacokinetic properties

Metyrapone is rapidly absorbed and eliminated from the plasma after oral administration

Absorption

Peak plasma concentrations are usually reached one hour after oral administration.

Distribution
After administration of 750 mg mean peak plasma concentrations are 3.7 microg/ml falling to 0.5 microg/ml 4 hours after administration.

Biotransformation
Metyrapol, the reduced form of metyrapone, is the main active metabolite. Eight hours after a single oral dose, the ratio of metyrapone in the plasma is 1: 1.5. Metyrapol takes about twice as long as metyrapone to be eliminated in the plasma.

Elimination
The plasma elimination half-life of metyrapone is about 2 hours after oral administration. Seventy–two hours after a first daily dose of 4.5 g Metopirone (750 mg every 4 hours), 5.3% of thetotal dose was excreted in the urine as metyrapone (9.2% in free form and 90.8% conjugated with glucuronic acid), and 38.5% in the form of metyrapol, the principal active metabolite (8.1% in free form and 91.9% conjugated with glucuronic acid).

5.3 Preclinical safety data

Preclinical data for Metopirone (metyrapone) reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity. Metyrapone was not mutagenic and genotoxic in in vitro and in vivo test systems. Animal reproduction studies adequate to evaluate teratogenicity and postnatal development have not been conducted with Metopirone. Metyrapone inhibits testosterone synthesis in male rodents, dogs and non-human primates, and affects steroidogenesis in rat ovarian granulosa and thecal cells. These effects were abolished in animals co-administered with metyrapone and corticosterone, and were therefore attributed to metyrapone inhibition of corticosterone synthesis.
Treatment of male dogs and langurs with metyrapone for 40 or 30 days, respectively, caused a marked loss of spermatogonia, spermatocytes and spermatozoa. Young mice (30 days old) treated with metyrapone for 21 days showed underdeveloped uteri, as well as atretic tertiary follicles in the ovary. The relevance of these findings for Cushing's syndrome patients is currently not clear. In a rabbit study, metyrapone has been shown to cross the placenta. Currently there are no available non-clinical studies conducted to investigate the carcinogenic potential of Metopirone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylvanillin
Gelatin
Glycerol
Macrogol 400
Macrogol 4000
P-methoxy acetophenone
Sodium ethyl parahydroxybenzoate (E215)
Sodium propyl parahydroxybenzoate (E217)
Titanium dioxide (E171)
Purified water

Printing Ink (Red):
Carminic acid (E120)

Aluminium chloride hexahydrate
Sodium hydroxide
Hypromellose
Propylene glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years
After opening: 2 months

6.4 Special precautions for storage

Keep the bottle tightly closed in order to protect from moisture.
Store below 25°C.

6.5 Nature and contents of container

HDPE (high-density polyethylene) bottle with tamper evident screw cap containing 50 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

HRA Pharma Rare Diseases
200 avenue de Paris
92320 CHATILLON
France

8. MARKETING AUTHORISATION NUMBER

[Assigned nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorization: 01 April 1979
Date of last renewal: 23 April 2019

10. DATE OF REVISION OF THE TEXT

14 April 2022