SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metopirone 250

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metyrapone 250mg

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

Yellowish-white, oblong, opaque, soft gelatin capsules printed 'HRA' on one side in red ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As a diagnostic test for ACTH insufficiency and in the differential diagnostic 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 250. The patient is given 30 mg/kg (maximum 3 g Metopirone 250) at midnight with yoghurt or milk to minimize 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 250 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 minimize nausea and vomiting.

Evaluation:

ACTH deficiency:
If the anterior pituitary is functioning normally, Metopirone 250 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 250 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 1,000 mg/day depending on the severity of hypercortisolism and the cause of Cushing's syndrome. Metyrapone 250 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.

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 Metopirone or to any of the excipients

4.4 Special warnings and precautions for use

Diagnostic applications
The metyrapone diagnostic test should be restricted to hospital.

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 damage delaying 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
Supervision

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 ectopic Cushing's syndrome
Patients with ectopic Cushing's syndrome are at risk for opportunistic infections such as Pneumocystis jirovecii pneumonia during Metopirone treatment. Appropriate prophylactic treatment may be considered in this population.

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

Breast-feeding
There is insufficient information on the excretion of metyrapone in human milk. A risk tonewborns/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 and sodium propyl parahydroxybenzoate can cause allergic reactions, which might be delayed.
This medicine contains less than 1 mmol sodium (23mg) 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 clearly necessary (in this case, blood pressure should be monitored and hypertension managed appropriately) and in women of childbearing potential not using contraception.

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

Adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, 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). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1. Adverse drug reactions

Blood and the lymphatic system disorders	
Not known:	Leukopenia, anaemia, thrombocytopenia
Endocrine disorders	
Rare:	Adrenal insufficiency,
Nervous system disorders	
Common:	Dizziness, sedation, headache
Vascular disorders	
Common:	Hypotension
Not known:	Hypertension
Gastrointestinal disorders	
Common:	Nausea, vomiting
Rare:	Abdominal pain
Skin and subcutaneous tissue disorders	
Rare:	Hirsutism, Allergic dermatitis
Not known:	Alopecia

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Signs and symptoms: The clinical picture of acute Metopirone poisoning is characterised by gastrointestinal symptoms and acute adrenocortical insufficiency.

Laboratory findings: hyponatraemia, hypochloraemia, and hyperkalaemia. In patients under treatment with insulin or oral antidiabetics, 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 and 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, 11β-hydroxylation 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 administrationof 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 Metopirone is about 2 hours after oral administration. Seventy-two hours after a first daily dose of 4.5g Metopirone (750mg every 4 hours), 5.3% of the total 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

Pre-clinical 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 (30days 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

Capsule contents: polyethylene glycol 400, glycerol 85%, purified water and polyethylene glycol 4000.

Capsule shell: gelatin, glycerol 85%, titanium dioxide, sodium ethyl parahydroxybenzoate, ethyl vanillin, sodium propyl parahydroxybenzoate, paramethoxy acetophenone, Phsal 53 MCT

6.2 Incompatibilities

None stated.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

High density polyethylene bottles of 50 capsules with child resistant polypropylene closure.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

CTS Ltd., 4 Haharash St.,
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8 MANUFACTURER

HRA Pharma Rare Diseases
200 avenue de Paris 92320 Chatillon
France

9 MARKETING AUTHORISATION NUMBER

068-34-23659-01

Revised in 11/2021 according to Ministry of Health guidelines.