SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT
Metopirone® Capsules 250mg

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
Metyrapone BP 250mg.

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
A diagnostic aid in the differential diagnosis of ACTH-dependent Cushing’s syndrome. The management of patients with Cushing’s syndrome.

In conjunction with glucocorticosteroids in the treatment of resistant oedema due to increased aldosterone secretion in patients suffering from cirrhosis, nephrosis and congestive heart failure.

4.2  Posology and method of administration

Adults:

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

For use as a diagnostic aid: the patient must be hospitalised. Urinary 17-oxygenic steroid excretion is measured over 24 hours on each of 4 consecutive days. The first 2 days serve as a control period. On the third day, 750mg Metopirone (3 capsules) must be given at four-hourly intervals to give a total of 6 doses (ie 4.5g). Maximum urine steroid excretion may occur on the fourth day. If urinary steroid excretion increases in response to Metopirone, this suggests the high levels of circulatory cortisol are due to adrenocortical hyperplasia following excessive ACTH production rather than a cortisol-producing adrenal tumour.
For therapeutic use: for the management of Cushing’s syndrome, the dosage must be adjusted to meet the patient’s requirements; a daily dosage from 250mg to 6g may be required to restore normal cortisol levels.

For the treatment of resistant oedema: The usual daily dose of 3g (12 capsules) should be given in divided doses in conjunction with a glucocorticoid.

Children: Children should be given a smaller amount based upon 6 four-hourly doses of 15mg/kg, with a minimum dose of 250mg every four hours.

Elderly: Clinical evidence would indicate that no special dosage regimen is necessary.

4.3 Contraindications
Primary adrenocortical insufficiency. Hypersensitivity to Metopirone or to any of the excipients. Pregnancy.

4.4 Special warnings and precautions for use

In relation to use as a diagnostic aid: anticonvulsants (eg phenytoin, barbiturates), anti-depressants and neuroleptics (eg amitriptyline, chlorpromazine), hormones that affect the hypothalamo-pituitary axis and anti-thyroid agents 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.

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.

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

The ability of the adrenal cortex to respond to exogenous ACTH should be demonstrated before Metopirone is employed as a test, as Metopirone may induce acute adrenal insufficiency in patients with reduced adrenal secretory capacity, as well as in patients with gross hypopituitarism.

Patients with liver cirrhosis often show a delayed response to Metopirone, due to liver damage delaying the metabolism of cortisol.

In cases of thyroid hypofunction, urinary steroid levels may rise very slowly, or not at all, in response to Metopirone.

Patients with ectopic Cushing’s syndrome are at risk from opportunistic infections such as Pneumocystis Jirovecii pneumonia (previously termed Pneumocystis carinii
pneumonia) during Metopirone treatment. Appropriate prophylactic treatment may be considered in this population.

When Metopirone is used as ACTH suppression test a diminished response was observed during pregnancy.

4.5 Interaction with other medicinal products and other forms of interaction

Anticonvulsants (e.g. phenytoin, barbiturates), psychotropic drugs (e.g. amitriptyline, chlorpromazine, alprazolam), hormone preparations, corticosteroids, antithyroid agents and cyproheptadine may affect the results of the Metopirone test (see Section 4.4, Special warnings and precautions for use).

Metopirone may potentiate paracetamol (acetaminophen) toxicity in humans.

4.6 Fertility, pregnancy and lactation

Pregnancy
Unless the potential benefit outweighs the risk to the foetus Metopirone should not be given to pregnant women, since the drug can impair the biosynthesis of foetal-placental steroids. Animal reproduction studies adequate to evaluate teratogenicity and postnatal development have not been conducted with Metopirone (see section 5.3 Preclinical safety data).

Lactation
Since it is not known whether metyrapone passes into the breast milk, Metopirone should not be given to breast-feeding women.

Fertility
No data are available from animal reproduction studies.

4.7 Effects on ability to drive and use machines
Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness and sedation.

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: Bone marrow failure

Endocrine disorders
Rare: Adrenal insufficiency, Hypoadrenalism

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

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, 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. Gastric lavage and forced emesis should be employed to reduce the absorption of the drug. 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 inhibits the enzyme responsible for the 11β-hydroxylation stage in the biosynthesis of cortisol and to a lesser extent, aldosterone. The fall in plasma concentration of circulating glucocorticoids stimulates ACTH secretion, via the feedback mechanism which accelerates steroid biosynthesis. As a result, 11-desoxycortisol, the precursor of cortisol, is released into the circulation, metabolised by the liver and excreted in the urine. Unlike cortisol, 11-desoxycortisol does not suppress ACTH secretion and its urinary metabolites may be measured.

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. Peak plasma levels usually occur one hour after ingestion of Metopirone; after a dose of 750mg Metopirone, plasma drug levels average 3.7μg/ml. Plasma drug levels decrease to a mean value of 0.5μg/ml 4 hours after dosing. The half-life of elimination of Metopirone from the plasma is 20 to 26 minutes.

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

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 (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. Metopirone was not mutagenic with or without metabolic activation in three strains of bacteria. Animal reproduction studies adequate to evaluate teratogenicity and postnatal development have not been conducted with Metopirone. Currently, there are no available non-clinical studies conducted to investigate the genotoxicity, or carcinogenic potential of Metopirone.

Effects in pre-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule contents: Glycerin, polyethylene glycol 400, polyethylene glycol 4000 and water. Capsule shell: Sodium ethylparaben, ethyl vanillin, gelatin, glycerin 85%, p-methoxy acetophenone, sodium propylparaben and titanium oxide (E171).

6.2 Incompatibilities
None stated.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Protect from moisture and heat. Store below 30°C.

6.5 Nature and contents of container
High density polyethylene bottles of 100 capsules with child resistant polypropylene closure.

6.6 Special precautions for disposal
None stated.

7 MARKETING AUTHORISATION HOLDER
Laboratoire HRA Pharma
15 rue Béranger
75003 Paris
France

8 MARKETING AUTHORISATION NUMBER(S)
PL 17836/0007
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25 June 1998

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