SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metyrapone HRA 250mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metyrapone BP 250mg.

Excipient(s) with known effect

Each capsule contains 0.71 mg of sodium ethylparaben (E215) and 0.35 mg sodium propylparaben (E217).

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

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

Posology

Adults

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 Metyrapone HRA (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 Metyrapone HRA, 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 beadjusted 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 dosesof 15mg/kg, with a minimum dose of 250mg every four hours.

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

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

Primary adrenocorticol insufficiency.

Hypersensitivity to Metyrapone 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 Metyrapone HRA test. If these drugs cannot be withdrawn, the necessity of carrying out the Metyrapone HRA test should be reviewed.

If adrenocortical or anterior pituitary function is more severely compromised than indicated by the results of the test, Metyrapone HRA may trigger transient adrenocortical insufficiency. This can be rapidly corrected by giving appropriate doses of corticosteroids.

Long-term treatment with Metyrapone HRA can cause hypertension as the result of excessivesecretion of desoxycorticosterone.

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

Patients with liver cirrhosis often show a delayed response to Metyrapone HRA, due to liverdamage delaying the metabolism of cortisol.

In cases of thyroid hypofunction, urinary steroid levels may rise very slowly, or not atall, in response to Metyrapone HRA.

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

When Metyrapone HRA is used as ACTH suppression test a diminished response wasobserved during pregnancy.

Excipients
Sodium ethylparaben (E215) and sodium propylparaben (E217) may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

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 agentsand cyproheptadine may affect the results of the Metyrapone HRA test (see Section 4.4, Special warnings and precautions for use).

Metyrapone HRA may potentiate paracetamol (acetaminophen) toxicity in humans.

4.6 Fertility, pregnancy and lactation

Pregnancy
Unless the potential benefit outweighs the risk to the foetus Metyrapone HRA 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 Metyrapone HRA (see section 5.3 Preclinical safety data).

Breast-feeding
Since it is not known whether metyrapone passes into the breast milk, Metyrapone HRA 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:	Leukopenia, anaemia, thrombocytopenia
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

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:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms: The clinical picture of acute Metyrapone HRA poisoning is characterised by gastrointestinal symptoms and acute adrenocortical insufficiency. Laboratory findings: hyponatraemia, hypochloraemia, hyperkalaemia. In patients undertreatment with insulin or oral antidiabetics, the signs and symptoms of acute poisoning with Metyrapone HRA 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 consideredif 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.

Metyrapone 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). Metyrapone HRA isused 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. Metyrapone 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 levelsusually occur one hour after ingestion of Metyrapone HRA; after a dose of 750mg Metyrapone HRA, 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 Metyrapone from the plasma is 20 to 26 minutes.

Metyrapol, the reduced form of metyrapone, is the main active metabolite. Eight hoursafter 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 Metyrapone HRA (750mg every 4 hours), 5.3% of the total dose was excreted in the urine as metyrapone (9.2% in free form and90.8% 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 Metyrapone HRA (metyrapone) reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity. Metyrapone HRA wasnot 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 Metyrapone HRA. Currently, there are noavailable non-clinical studies conducted to investigate the genotoxicity, or carcinogenic potential of Metyrapone HRA.

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 (E215), ethyl vanillin, gelatin, glycerin 85%, p-methoxy acetophenone, sodium propylparaben (E217) and titanium oxide (E171).

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years

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 100 capsules with child resistant polypropylene closure.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

HRA Pharma Rare Diseases
200 avenue de Paris
92320 CHATILLON
France

8 MARKETING AUTHORISATION NUMBER(S)

PL 51757/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 June 1998

10 DATE OF REVISION OF THE TEXT

28/06/2022