SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metyrapone Esteve 250mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metyrapone BP 250mg.

Excipient(s) with known effect

Each capsule contains 0.71 mg of sodium ethyl parahydroxybenzoate (E215) and 0.35 mg sodium propyl parahydroxybenzoate (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

Metyrapone Esteve is indicated as a diagnostic aid for ACTH insufficiency and in the differential diagnosis of ACTH-dependent Cushing's syndrome.

Metyrapone Esteve is indicated for the management of patients with endogenous 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

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 Metyrapone Esteve. The patient is given 30 mg/kg (maximum 3 g Metyrapone Esteve) at midnight with yoghurt or milk to minimise nausea and vomiting.

Patients with suspected adrenocortical insufficiency should be hospitalised overnight as a precautionary measure.

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 11-desoxycortisol to over 0.2 micromol/L (70 microg/L).
Healthy individuals have an ACTH response of 42 to 690 pg/mL (9 to 210 pmol/L). In general, patients with partial secondary adrenal insufficiency have ACTH responses from 10 to 200 pg/mL (2 to 44 pmol/L), while patients with primary adrenal insufficiency have higher responses. Because of this overlap, the ACTH response alone cannot be used to distinguish between healthy individuals and those with adrenal insufficiency.

(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 Metyrapone Esteve 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. Maximum urine steroid excretion may occur on the fourth day. If urinary steroid excretion increases in response to Metyrapone Esteve, this suggests the high levels of circulatory cortisol are due to adrenocortical hyperplasia following excessive ACTH production rather than a cortisol- producing adrenal tumour.

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, Metyrapone Esteve 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 Metyrapone Esteve 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 usual maintenance dose varies between 500 and 6000 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.

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.

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 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 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 Metyrapone Esteve is employed as a test, as Metyrapone Esteve 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.

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 Metyrapone Esteve. Before the Metyrapone Esteve 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, Metyrapone Esteve may trigger transient adrenocortical insufficiency. This can be rapidly corrected by giving appropriate doses of corticosteroids.

Reduced liver function
Patients with liver cirrhosis often show a delayed response to Metyrapone Esteve, due to liver damage delaying the metabolism of cortisol.

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 Metyrapone Esteve 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 Metyrapone Esteve 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 is warranted Initiation of an appropriate prophylactic treatment may be considered.

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

Hypokalaemia
Hypokalaemia can occur in patients with Cushing's syndrome and during Metyrapone Esteve treatment. Potassium levels should be checked before therapy start and monitored periodically during therapy. Any hypokalaemia prior to Metyrapone Esteve 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 Metyrapone Esteve, monitoring of ECG and electrolytes are recommended.

Excipients
The presence of the excipients sodium ethyl parahydroxybenzoate (E215) and sodium propyl parahydroxybenzoate (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

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 Metyrapone Esteve test.

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

Anticipated interactions

Metyrapone Esteve 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). Metyrapone Esteve 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 Metyrapone Esteve 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 Metyrapone Esteve..

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

Metyrapone Esteve has minor influence on the ability to drive and use machines. Since Metyrapone Esteve 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			Leukopenia, anaemia, thrombocytopenia

disorders			
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 Yellow Card Scheme at 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 Esteve 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 Esteve 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 Esteve 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 Esteve 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. Metyrapone Esteve may also suppress biosynthesis of aldosterone, resulting in mild natriuresis.

5.2 Pharmacokinetic properties

Metyrapone is rapidly absorbed and eliminated from the plasma.
Absorption
Peak plasma levels usually occur one hour after ingestion of Metyrapone Esteve;
Distribution
after a dose of 750mg Metyrapone Esteve, plasma drug levels average 3.7µg/ml. Plasma drug levels decrease to a mean value of 0.5µg/ml 4 hours after dosing.
Biotransformation
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.
Elimination
The half-life of elimination of Metyrapone Esteve from the plasma is about 2 hours after oral administration.Seventy-two hours after a first daily dose of 4.5g Metyrapone Esteve (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

Non-clinical data 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 Metyrapone Esteve. 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 Metyrapone Esteve.

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 andwater.
Capsule shell: Sodium ethyl parahydroxybenzoate (E215), ethyl vanillin, gelatin, glycerin 85%, p- methoxy acetophenone, sodium propyl parahydroxybenzoate (E217) and titanium oxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

No special requirements

7 MARKETING AUTHORISATION HOLDER

Esteve RD France SAS
25 Boulevard Romain Rolland
92120 Montrouge
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

21/02/2025