NEW ZEALAND DATA SHEET

1. METOPIRONE® 250 mg, Capsules

Metopirone 250 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg metyrapone

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules for oral administration.

Capsules containing 250 mg active substance with colourless, viscous to jelly-like contents, branded HRA with red ink on one side. The yellowish/white opaque capsules are approximately 18.5mm in length and 7.5mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metopirone is a diagnostic drug for testing the function of the anterior pituitary-adrenal axis. It can also be used for therapeutic purposes.

Diagnostic applications

- Diagnosis of latent ACTH deficiency:

The Metopirone test can only be employed if the adrenal cortex responds normally to ACTH, i.e. if morning cortisol and/or cortisol values as determined by the Synacthen® test are within, or at least very close to, the normal range.

The test can be used:

  - in confirmed disturbances of pituitary function or suspected pituitary tumours, and before and after surgery in the pituitary region;
  - to assess ACTH suppression during or after glucocorticoid therapy.

- Differential diagnosis of adrenocortical hyperactivity in Cushing's syndrome

Therapeutic applications

Metopirone can be employed as supplementary therapy in conditions associated with overproduction of glucocorticoids and mineralocorticoids, particularly when causal treatment is not possible.

- Cushing's syndrome, especially when related to adrenal tumours
- Hyperaldosteronism, resistant oedema

4.2 Dosage and method of administration

Dose

Diagnostic applications

Single-dose short test to diagnose latent ACTH deficiency.

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. The same dose is recommended in children. The blood sample for the assay is taken early the following morning (7.30 to 8.00). 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 micrograms/L). Patients with suspected adrenocortical insufficiency should be hospitalised overnight as a precautionary measure, although no cases of acute adrenocortical insufficiency have been reported to date in association with the single-dose short test.

Multiple-dose test to diagnose latent ACTH deficiency and for differential diagnosis of adrenocortical hyperactivity in Cushing's syndrome.

The patient must be hospitalised. In this test, urinary steroid levels are measured. First, baseline values are determined for the 24 hours preceding the test. Then 500 to 750 mg Metopirone is administered every 4 hours for 24 hours, giving a total dose of 3.0 to 4.5 g. 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. The maximum effect of Metopirone on urinary steroid values should be reached within the next 24 hours.

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 overproduction 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 applications

Cushing's syndrome, especially when related to adrenal tumours: the dosage should be adapted to the individual patient's needs. The dosage required to normalise cortisol values ranges from 250 mg to 6 g daily.

Hyperaldosteronism, resistant oedema: the usual daily dosage is 3 g Metopirone given in divided doses. In the case of hyperaldosteronism, Metopirone should be given with a glucocorticoid. In resistant oedema Metopirone has been used in combination with a diuretic therapy and for short periods of time.

Method of Administration

Metopirone is administered orally.

4.3 Contraindications

Manifest primary adrenocortical insufficiency; hypersensitivity to metyrapone or to any of the excipients.

4.4 Special warnings and precautions for use

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 gross hypopituitarism.

Metopirone can cause hypertension due to excessive secretion of desoxycorticosterone.

Before the Metopirone test is carried out, drugs affecting pituitary or adrenocortical function should be discontinued (see "Interactions with other drugs and other types of interaction"). 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.

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.

Since the plasma elimination half-life of cortisol is longer when hepatic function is impaired, patients with liver cirrhosis often respond to Metopirone more slowly.

In patients with hypothyroidism, the Metopirone-induced increase in steroid values may be delayed or absent.

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

4.5 Interactions with other medicines and other forms of interaction

Observed Interactions

Anticonvulsants (e.g. phenytoin, barbiturates), psychotropic drugs (e.g. amitriptyline, chlorpromazine, and alprazolam), hormone preparations, corticosteroids and antithyroid agents may affect the results of the Metopirone test.

Anticipated Interactions

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.

Breast-feeding

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

Since Metopirone may cause dizziness and sedation, patients should exercise caution when driving or operating machinery

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,
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 suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Signs and symptoms

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

Laboratory findings: hyponatraemia, hypochloraemia, hyperkalaemia.

Treatment

There is no specific antidote. In addition to general measures to eliminate the drug and reduce absorption, a large dose of hydrocortisone should be administered at once, together with saline and glucose infusions.

For a few days blood pressure and fluid and electrolyte balance should be monitored.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Metyrapone inhibits adrenocorticosteroid synthesis. It reduces cortisol and corticosterone production by inhibiting the 11-beta-hydroxylation reaction in the adrenal cortex. Removal of the strong inhibitory feedback mechanism exerted by cortisol results in an increase in adrenocorticotropic 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 1 hour after administration.

Distribution

After administration of 750 mg, mean peak plasma concentrations are 3.7 micrograms/mL, falling to 0.5 micrograms/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 to metyrapol in the plasma is 1:1.5. Metyrapol takes about twice as long as metyrapone to be eliminated from the plasma.

Elimination

The plasma elimination half-life of metyrapone is 20 to 26 minutes. After administration of 4.5 g metyrapone (750 mg every 4 hours), an average of 5.3% of the dose was excreted in the urine in the form of metyrapone (9.2% free and 90.8% glucuronised) and 38.5% in the form of metyrapol (8.1% free and 91.9% glucuronised) within 72 hours after the first dose was given.

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

Sodium salt of ethyl parahydroxybenzoate (E215), ethylvanillin, gelatin, glycerol, p-methoxy acetophenone, macrogol 400, macrogol 4000, sodium salt of propyl parahydroxybenzoate (E217), titanium dioxide, red ink

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

Store below 25°C. Protect from moisture and heat.

6.5 Nature and Contents of Container

Bottles of 50 capsules

6.6 Special Precautions for Disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics

58 Richard Pearse Drive

Airport Oaks

Mangere

AUCKLAND

For New Zealand Medical Information enquiries free-call 0800138803

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

7 March 2019

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat to new Medsafe data sheet template
6.3	Revision of storage conditions