AUSTRALIAN PRODUCT INFORMATION – METOPIRONE® (METYRAPONE) SOFT CAPSULE

1. NAME OF THE MEDICINE

Metyrapone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

METOPIRONE is supplied as soft gelatin capsules each containing 250 mg of metyrapone.

Excipients with known effects: sodium ethyl hydroxybenzoate, sodium propyl hydroxybenzoate.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

METOPIRONE capsules 250 mg are white to yellowish white oblong soft gelatin capsules marked HRA on one side in red ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diagnostic use

- For the diagnosis of latent ACTH deficiency such as in cases of known pituitary dysfunction or of a suspected pituitary tumour, as well as before and after surgical intervention in the region of the pituitary; and, to assess the degree of ACTH suppression during or after glucocorticoid therapy.

- For the differential diagnosis of states of adrenocortical hyperfunction in Cushing's Syndrome.

4.2 Dose and method of administration

Dose as a diagnostic agent

i) Short single dose test (which can be carried out in ambulant patients) for the diagnosis of latent ACTH deficiency

Adults

In the short single-dose test, 11-desoxycortisol (Compound S) and/or ACTH are determined in the plasma following a single dose of METOPIRONE. At around midnight, the patient is given 30 mg/kg (maximum 3 g metyrapone).

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.

Paediatric population

The same dose as in adults is recommended in children.

Assessment

The accepted normal values employed will depend on the method used for assaying ACTH and 11-desoxycortisol and may vary in different laboratories. A rise in plasma ACTH to at least 44 pmol/litre (200 ng/litre), or in 11-desoxycortisol to over 0.2 µmol/litre (70 µg/litre), usually indicates a normal ACTH reserve.

Patients in whom adrenocortical insufficiency is suspected, and who cannot be adequately supervised at home, should be hospitalised for the night as a precautionary measure.

ii) Multiple dose test (which can only be carried out in hospital) for the diagnosis of latent ACTH deficiency and the differential diagnosis of states of adrenocortical hyperfunction in Cushing's Syndrome

Adults

The patient must be hospitalised. The urinary excretion of steroids is measured. First, baseline values are determined for the 24 hours preceding the test. Then, on the second day, 500 to 750 mg metyrapone is administered every 4 hours for 24 hours, to a total of 3.0 to 4.5 g.

The effect is evaluated in two consecutive 24-hour urinary samples. The effect on the urinary steroid values can be expected to reach its maximum within this 24-hour period.

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.

Assessment

ACTH deficiency: When the anterior pituitary is functioning normally METOPIRONE causes a pronounced increase (to double or more) in the urinary excretion of 11-desoxycortisol and other 11-desoxycorticosteroids. The absence of such an increase indicates secondary adrenocortical insufficiency.

Cushing's syndrome: If the urinary excretion of 11-desoxycorticosteroids increases in response to METOPIRONE, this indicates that excessive production of ACTH has led to adrenocortical hyperplasia (Cushing's disease). Such an increase can be taken as a sign that there is no adrenocortical tumour producing cortisol autonomously.

Method of administration

Oral administration.

It is recommended that the capsules be taken together with yoghurt or milk or after meals to minimise nausea and vomiting which can lead to impaired absorption.

4.3 Contraindications

- Adrenocortical insufficiency
- Hypersensitivity to metyrapone or to any of the excipients listed in section 6.1 List of excipients.

4.4 Special warnings and precautions for use

The metyrapone multiple dose diagnostic test should be restricted to the hospital setting.

Identified precautions

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.

Patients taking drugs affecting the hypothalamo-pituitary adrenal axis

Before the METOPIRONE test is carried out, drugs affecting pituitary or adrenocortical function should be discontinued (see section 4.5 Interactions with other medicines and other forms of interactions).

In cases where adrenocortical or anterior pituitary function is more severely impaired, METOPIRONE may provoke transient adrenocortical insufficiency. This can be rapidly overcome by administering a corticosteroid.

Patients with hypothyroidism

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

Opportunistic infections

Patients with severe Cushing's syndrome are at risk for opportunistic infections such as *Pneumocystis Jirovecii* pneumonia during METOPIRONE treatment. 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 METOPIRONE can cause hypertension or worsen existing hypertension due to excessive secretion of desoxycorticosterone.

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 (23 mg) per capsule. It is essentially 'sodium free'.

Use in hepatic impairment

Patients with liver cirrhosis often show a delayed response to METOPIRONE, because the liver damage results in prolonging the plasma elimination half-life of cortisol.

Use in the elderly

Clinical studies of METOPIRONE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

Clinical evidence would indicate that no special dosage regimen is required. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Paediatric use

Refer to section 4.2 Dose and method of administration.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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:

Anticonvulsants (e.g. phenytoin, barbiturates), psychoactive drugs (e.g. amitriptyline, chlorpromazine and alprazolam), hormone preparations that affect the hypothalamo-pituitary axis, corticosteroids, cyproheptadine and anti-thyroid agents may exert an influence on 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

Effects on fertility

The effect of METOPIRONE on human fertility has not been investigated in clinical studies. No dedicated animal fertility studies have been conducted with metyrapone. In repeat-dose toxicity studies, metyrapone has been shown to cause adverse effects on spermatogenesis (loss of spermatogonia, spermatocytes and spermatozoa in dogs at 20 mg/kg/day intraperitoneally [IP]) and ovarian follicular development (reduced ovary and uterus weights, underdeveloped uterus in mice at 100 mg/kg/day IP). Metyrapone can decrease reproductive hormones by targeting adrenal androgenesis.

Use in pregnancy (Category B3)

There are no adequate data on the use of METOPIRONE in pregnant women.

METOPIRONE is not recommended during pregnancy when used as a diagnostic test unless the potential benefit outweighs the risks clearly necessary (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.

Human data

The METOPIRONE test was administered to pregnant women in their second and third trimester of pregnancy and evidence was found that the fetal pituitary responded to the enzymatic block. Transplacental passage of METOPIRONE has been shown in humans. There are a few published reports of low cortisol levels at birth in infants exposed *in utero* following chronic use of metyrapone in pregnant females.

Animal data

Maternal administration of metyrapone during pregnancy caused reduction in implantations and increased fetal malformation in mice (40 mg/kg/day SC). Embryofetal effects were seen in rats at a cumulative dose of at least 60 mg/animal SC over 1 or 2 days (adrenal hypertrophy, reduced serum corticosterone levels) during the period of organogenesis. Transplacental passage of metyrapone has been shown in rabbits.

Use in lactation

There is insufficient information on the presence of metyrapone in human milk, the effects on the breastfed infant, or the effects on milk production. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with METOPIRONE.

4.7 Effects on 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 Adverse effects (Undesirable effects)

Adverse drug reactions 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.

Blood and the lymphatic system disorders

Not known: Leukopenia, anaemia, thrombocytopenia

Endocrine disorders

Rare: Adrenal insufficiency

Nervous system disorders

Common: Dizziness, sedation, headache

Not known: Light-headedness

Vascular disorders

Common: Hypotension

Not known: Hypertension

Gastrointestinal disorders

Common: Nausea, vomiting

Rare: Abdominal pain

Skin and subcutaneous tissue disorders

Rare: Allergic skin reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Signs and symptoms

The clinical picture of overdosage with METOPIRONE is characterised by gastrointestinal symptoms and signs of 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. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Mechanism of action

METOPIRONE inhibits reversibly the biosynthesis of cortisol, corticosterone, and aldosterone in the adrenal cortex by blocking enzymatic 11-beta-hydroxylation in the steroid ring. In the normal person, a compensatory increase in ACTH release follows and the secretion of 11-desoxycortisol, 11-desoxycorticosterone and 17-hydroxycorticoids is markedly accelerated.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Metyrapone is rapidly absorbed after administration by mouth and is also rapidly eliminated from the plasma. Peak concentrations are usually attained in plasma 1 hour after ingestion of METOPIRONE.

Distribution

Following a dose of 750 mg, the mean peak concentration is 3.7 µg/mL and decreases to a mean value of 0.5 µg/mL 4 hours after ingestion.

Metabolism

The plasma elimination half-life of metyrapone is about 2 hours after oral administration. Metyrapol (reduced metyrapone) is the principal active metabolite. The metyrapone / metyrapol ratio in the plasma 8 hours after a single oral dose is 1/1.5.

Excretion

Following a total dosage of 4.5 g metyrapone (750 mg every 4 hours), the quantities excreted in the urine 72 hours after the first dose averaged 5.3% of the total dosage in the form of 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

Genotoxicity

No studies for genotoxicity have been performed with METOPIRONE.

Carcinogenicity

No studies for carcinogenicity have been performed with METOPIRONE.

Teratogenicity

Animal reproduction studies, adequate to evaluate teratogenicity and postnatal development, have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

It also contains sodium ethyl hydroxybenzoate, ethyl vanillin, gelatin, glycerol, acetanisole, Macrogol 400, Macrogol 4000, sodium propyl hydroxybenzoate, titanium dioxide, purified water and Edible ink Red (PI 3115) as excipients.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Protect from moisture. Keep out of the reach and sight of children.

6.5 Nature and contents of container

Each HDPE bottle with polypropylene child resistant closure with a liner for induction seal contains 50 capsules.

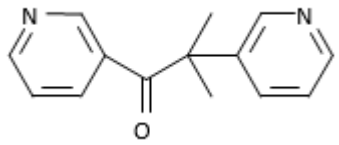
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Chemical name: 2-methyl-1,2-di-3-pyridyl-1-propanone
Molecular formula: $C_{14}H_{14}N_2O$
Molecular weight: 226.27 g/mol
Structural formula:



CAS number

54-36-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (S4) Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

2 August 1991

10. DATE OF REVISION

04 July 2023

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Summary table of changes

Section Changed	Summary of New Information
4.2	Clarification of dosing information
4.4	Addition of information for adrenal insufficiency, excipients and use in the elderly
4.5	Addition of precautions for potential interactions
4.6	Updated fertility, pregnancy and lactation information
4.7	Updated information
4.8	Addition of leukopenia, anaemia and thrombocytopenia Deletion of bone marrow failure, hirsutism and alopecia
4.9	Updated treatment recommendations in acute poisoning