

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

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

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 for diagnostic applications

(i) Single-dose short test to diagnose latent ACTH deficiency

Adults

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. At around midnight, the patient is given 30 mg/kg (maximum 3 g metyrapone).

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.

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

Paediatric population

The same dose is recommended in children.

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).

(ii) Multiple-dose test - diagnosis of ACTH insufficiency and differential diagnosis of adrenocortical hyperfunction in Cushing's syndrome

Adults

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, on the second day, 500 to 750 mg metyrapone is administered every 4 hours for 24 hours, giving a total dose of 3.0 to 4.5 g.

The effect is evaluated in two consecutive 24-hour urinary samples. The maximum effect on urinary steroid values should be reached within the next 24 hours.

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.

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.

Dose for therapeutic applications

Adults

Cushing's syndrome

For the management of Cushing's syndrome, the initial dose of metyrapone may vary from 250 to 1,500 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 1,500 mg/day.

Lower starting doses may be used in cases of mild Cushing's disease or adrenal adenoma or hyperplasia. The dosage of metyrapone should be adjusted on an individual basis to meet patient's requirements and depending on tolerability.

The usual maintenance dose varies between 500 and 6,000 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.

Hyperaldosteronism, resistant oedema

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

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 indicates that no special dosage recommendations are required in all indications.

Method of administration

Oral administration.

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

4.3 Contraindications

- Manifest primary adrenocortical insufficiency
- Hypersensitivity to metyrapone or to any of the excipients listed in [section 6.1](#).

4.4 Special warnings and precautions for use

Diagnostic applications

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.

Reduced liver function

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

Patients with hypothyroidism

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

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](#)).

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.

Therapeutic applications

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

METOPIRONE 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 METOPIRONE 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 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 as the result of excessive secretion of desoxycorticosterone.

Hypokalaemia

Hypokalaemia can occur in patients with Cushing's syndrome and during METOPIRONE treatment. Potassium levels should be checked before therapy start and monitored periodically during therapy.

Any hypokalaemia prior to METOPIRONE 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 METOPIRONE, monitoring of ECG and electrolytes are recommended.

Excipients

The presence of the excipients sodium ethyl parahydroxybenzoate (E215) and sodium propyl parahydroxybenzoate (E217) 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'.

4.5 Interactions with other medicines 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), antidepressants and neuroleptics (e.g. amitriptyline, chlorpromazine, and alprazolam), hormones that affect the hypothalamo-pituitary axis, corticosteroids, antithyroid agents and cyproheptadine may affect 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

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. METOPIRONE 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 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.

Transplacental passage of metyrapone has been shown in animals and humans. Therefore, if METOPIRONE 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 METOPIRONE.

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.

4.7 Effects on ability to drive and use machines

METOPIRONE has a minor influence on the 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 listed according to system organ classes and ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) 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

System Organ Class	Frequency SOC / Preferred Term		
	Very common ($\geq 1/10$)	Common ($\geq 1/100$, $< 1/10$)	Not known
Blood and lymphatic system disorders			Leukopenia Anaemia Thrombocytopenia
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	
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

Description of selected adverse reactions

Opportunistic infections, such as *Pneumocystis jirovecii* pneumonia, have been described in literature and spontaneous reports. Frequency is unknown. (See [section 4.4](#)).

Reporting of suspected adverse reactions

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. 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 infusions. 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 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

Mechanism of action

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 adrenocorticotrophic 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

Absorption

Metyrapone is rapidly absorbed and eliminated from the plasma after oral administration. 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 about 2 hours after oral administration. 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

Preclinical 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 preclinical 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 ethyl parahydroxybenzoate (E215), ethyl vanillin, gelatin, glycerol, acetanisole, macrogol 400, macrogol 4000, sodium propyl parahydroxybenzoate (E217), titanium dioxide purified water and red ink. The red ink contains carmine (E120), aluminium chloride hexahydrate, sodium hydroxide and hypromellose.

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

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

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9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

10 August 2022

Summary Table of Changes

Section Changed	Summary of New Information
4.2	Addition of guidance for the adjustment of dose in the management of Cushing's syndrome
4.4	Addition on safety information for reduced liver function, hypocortisolism, assay methods, patients with severe Cushing's syndrome, hypertension, hypokalaemia, QTc prolongations and excipients
4.5	Addition of an interaction for cyproheptadine
4.6	Updated fertility, pregnancy and lactation information
4.7	Updated information
4.8	Revision of adverse events information based on the clinical and post-marketing data
4.9	Updated treatment recommendations in acute poisoning
All	Minor editorial changes for clarity