

Package Insert

1. Name of the product

Methyldopa Remedica 250 mg film-coated tablets

2. Name and Strength of Active Ingredient

Each film-coated tablet contains methyldopa equivalent to 250 mg anhydrous methyldopa.

3. Dosage form

Film-coated tablet.

Yellow, round, film-coated, with Remedica's logo on one side and embossed with "MD250" on the other side.

4. Pharmacological Properties

Pharmacodynamics

Pharmacotherapeutic group: antiadrenergic agents; ATC code: C02AB

Mechanism of action

It appears that several mechanisms of action account for the clinically useful effects of methyldopa and the current generally accepted view is that its principal action is on the central nervous system. The antihypertensive effect of methyldopa is probably due to its metabolism to alpha-methyl noradrenaline, which lowers arterial pressure by stimulation of central inhibitory alpha-adrenergic receptors, false neurotransmission, and/or reduction of plasma renin activity. Methyldopa has been shown to cause a net reduction in the tissue concentration of serotonin, dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline).

Pharmacokinetics

Absorption

Absorption of oral methyldopa is variable and incomplete.

Distribution

Bioavailability after oral administration averages 25%.

Biotransformation

Peak concentrations in plasma occur at two to three hours, and elimination of the drug is biphasic regardless of the route of administration. Plasma half-life is 1.8 ± 0.2 hours.

Elimination

Renal excretion accounts for about two thirds of drug clearance from plasma.

5. Clinical Particulars

Indications

For treatment of moderate to severe hypertension.

Posology and method of administration

Posology

The recommended dose is:

- Adults: Initial - Oral, 250 mg two or three times a day for two days, the dosage then being adjusted as directed.
- Maintenance: Oral, 500 mg to 2 g a day, divided into two to four doses, not exceeding 3 g daily.
- Children: Oral, initially 10 mg per kg of body weight daily, divided into two to four doses, the dosage then being adjusted as directed, not exceeding 65 mg per kg of body weight or 3 g daily, whichever is less

Method of administration

Oral administration.

Contraindications

Methyldopa is contraindicated in patients with:

- active hepatic disease, such as acute hepatitis and active cirrhosis.
- hypersensitivity to the active substance (including hepatic disorders associated with previous methyldopa therapy), or to any of the excipients contained in the product.
- depression.
- on therapy with monoamine oxidase inhibitors (MAOIs).
- with a catecholamine-secreting tumour such as pheochromocytoma or paraganglioma.
- with porphyria.

Warnings and Precautions

Acquired haemolytic anaemia has occurred rarely; should symptoms suggest anaemia, haemoglobin and/or haematocrit determinations should be made. If anaemia is confirmed, tests should be done for haemolysis. If haemolytic anaemia is present, Methyldopa should be discontinued. Stopping therapy, with or without giving a corticosteroid, has usually brought prompt remission. Rarely, however, deaths have occurred.

Reversible leucopenia, with primary effect on granulocytes has been reported rarely. The granulocyte count returned to normal on discontinuing therapy. Reversible thrombocytopenia has occurred rarely.

Occasionally, fever has occurred within the first three weeks of therapy, sometimes associated with eosinophilia or abnormalities in liver-function tests. Jaundice, with or without fever, also may occur. Its onset is usually within the first two or three months of therapy.

Should fever, abnormality in liver function, or jaundice occur, therapy should be withdrawn. If related to methyldopa, the temperature and abnormalities in liver function will then return to normal. Methyldopa should not be used again in these patients. Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction.

Patients may require reduced doses of anaesthetics when on methyldopa. If hypotension does occur during anaesthesia, it can usually be controlled by vasopressors. The adrenergic receptors remain sensitive during treatment with methyldopa.

Dialysis removes methyldopa; therefore, hypertension may recur after this procedure. Rarely, involuntary choreoathetotic movements have been observed during therapy with methyldopa in patients with severe bilateral cerebrovascular disease. Should these movements occur, therapy should be discontinued.

Interference with laboratory tests:

Methyldopa may interfere with the measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and AST (SGOT) by colorimetric method. Interference with spectrophotometric methods for AST (SGOT) analysis has not been reported.

As methyldopa fluoresces at the same wavelengths as catecholamines, spuriously high amounts of urinary catecholamines may be reported interfering with a diagnosis of catecholamine-secreting tumours such as phaeochromocytoma or paraganglioma.

It is important to recognise this phenomenon before a patient with a possible phaeochromocytoma is subjected to surgery. Methyldopa does not interfere with measurements of VMA (vanillylmandelic acid) by those methods which convert VMA to vanillin. Methyldopa is contraindicated for the treatment of patients with a catecholamine-secreting tumour such as phaeochromocytoma or paraganglioma.

Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites.

Interaction with other medicaments

Lithium

When Methyldopa and Lithium are given concomitantly the patient should be monitored carefully for symptoms of Lithium toxicity.

Other anti-hypertensive drugs

When methyldopa is used with other antihypertensive drugs, potentiation of antihypertensive action may occur. The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy.

Other classes of drugs

The antihypertensive effect of Methyldopa may be diminished by sympathomimetics, phenothiazines, tricyclic antidepressants and MAOIs (see 'Contraindications'). In addition, phenothiazines may have additive hypertensive effects.

Iron

Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulphate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa.

Pregnancy and Lactation

Pregnancy

Methyldopa has been used under close medical supervision for the treatment of hypertension during pregnancy. There was no clinical evidence that Methyldopa caused fetal abnormalities or affected the neonate.

Published reports of the use of methyldopa during all trimesters indicate that if this drug is used during pregnancy the possibility of fetal harm appears remote.

Methyldopa crosses the placental barrier and appears in cord blood.

Although no obvious teratogenic effects have been reported the possibility of foetal injury cannot be excluded and the use of the drug in women who are or may become pregnant, requires that anticipated benefits be weighed against possible risks.

Breast-feeding

Methyldopa appears in breast milk. The use of the drug in breast-feeding mothers requires that anticipated benefits be weighed against possible risks.

Side effects

The following convention has been utilised for the classification of frequency: Very common, common, uncommon, rare, very rare and not known (cannot be estimated from the available data).

System Organ Class	Adverse event term	Frequency
Infections and infestations	Sialoadenitis	Not known
Blood and lymphatic system disorders	Haemolytic anaemia, bone-marrow failure, leukopenia, granulocytopenia, thrombocytopenia, eosinophilia	Not known
Endocrine disorders	Hyperprolactinaemia	Not known
Psychiatric disorders	Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido	Not known
Nervous system disorders	Sedation (usually transient), headache, paraesthesia, Parkinsonism, VIIth nerve paralysis, choreoathetosis, mental impairment, carotid sinus syndrome, dizziness, symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)	Not known
Cardiac disorders	Bradycardia, angina pectoris, myocarditis, pericarditis, atrioventricular block	Not known
Vascular disorders	Orthostatic hypotension (decrease daily dosage)	Not known
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Not known
Gastrointestinal disorders	Nausea, vomiting, abdominal distension, constipation, flatulence, diarrhoea, colitis, dry mouth, glossodynia, tongue discolouration, pancreatitis	Not known
Hepatobiliary disorders	Liver disorders including hepatitis, jaundice	Not known
Skin and subcutaneous tissue disorders	Rash (eczema, lichenoid eruption), toxic epidermal necrolysis, angioedema, urticaria	Not known
Musculoskeletal and connective tissue disorders	Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia	Not known
Reproductive system and breast disorders	Breast enlargement, gynaecomastia, amenorrhoea, lactation disorder, erectile dysfunction, ejaculation failure	Not known
General disorder and administration site conditions	Asthenia, oedema (and weigh gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear). Pyrexia	Not known

Investigations	Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver function tests, increased blood urea	Not known
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Effects on ability to drive and use machines

Methyldopa may cause sedation, usually transient, during the initial period of therapy or whenever the dose is increased. If affected, patients should not carry out activities where alertness is necessary, such as driving a car or operating machinery.

Symptoms and Treatment of Overdose

Symptoms

Acute overdosage with Methyldopa may produce acute hypotension with other responses attributable to brain and gastro-intestinal malfunction (excessive sedation, weakness, bradycardia, dizziness, light-headedness, constipation, distension, flatus, diarrhoea, nausea and vomiting).

Management

If ingestion is recent, emesis may be induced or gastric lavage performed. There is no specific antidote. Methyldopa is dialysable. Treatment is symptomatic. Infusions may be helpful to promote urinary excretion. Special attention should be directed towards cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity.

Administration of sympathomimetic agents may be indicated. When chronic overdosage is suspected, Methyldopa should be discontinued.

6. Pharmaceutical Particulars

Storage conditions

Store below 30°C. Protect from light and moisture.

Shelf-life

5 years

Pack size available

Blister (PVC / PVDC – Aluminium). Pack sizes of 3x10's and 10x10's film-coated tablets.

Not all pack sizes may be marketed.

7. Manufacturer

Remedica Ltd.
Aharnon Street, Limassol Industrial Estate, 3056 Limassol, Cyprus

8. Product Registration holder

Eucogen Sdn. Bhd.,
No. 6A Jalan Sungai Burung U 32/U, Bukit Rimau Seksyen 32, 40460 Shah Alam
Selangor, Malaysia.

9. Date of revision of the text

12/2021

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