

Summary of Product Characteristics

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1. NAME OF THE MEDICINAL PRODUCT

Methyldopa Tablets BP 250mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Methyldopa BP eq. to

Anhydrous Methyldopa 250mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Yellow coloured, round, biconvex, film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of hypertension.

4.2 Posology and Method of administration

Posology

Use in adults and children over 12 years

Initial dosage: Usually 250mg two or three times a day, for two days.

Adjustment: Usually adjusted at intervals of not less than two days, until an adequate response is obtained. The maximum recommended daily dosage is 3g.

Many patients experience sedation for two or three days when therapy with Methyldopa is started or when the dose is increased. When increasing the dosage, therefore, it may be desirable to increase the evening dose first. Withdrawal of Methyldopa is followed by return of hypertension, usually within 48 hours. This is not complicated generally by an overshoot of blood pressure.

Patients with renal impairment

Methyldopa is largely excreted by the kidney, and patients with impaired renal function may respond to smaller doses.

Other antihypertensives

Therapy with Methyldopa may be initiated in most patients already on treatment with other antihypertensive agents by terminating these antihypertensive medications gradually, as required. Following such previous antihypertensive therapy, Methyldopa should be limited to an initial dose of not more than 500mg daily and increased as required at intervals of not less than two days.

When Methyldopa is given to patients on other antihypertensives the dose of these agents may need to be adjusted to effect a smooth transition.

When 500mg of Methyldopa is added to 50mg of hydrochlorothiazide, the two agents may be given together once daily.

Paediatric population: Children under 12 years: Initial dosage is based on 10mg/kg of bodyweight daily in 2-4 oral doses. The daily dosage is then increased or decreased until an adequate response is achieved. The maximum dosage is 65mg/kg or 3g daily, whichever is less.

Elderly: The initial dose in elderly patients should be kept as low as possible, not exceeding 250mg daily. An appropriate starting dose in the elderly would be 125mg twice daily increasing slowly as required, but not to exceed a maximum daily dosage of 2g. Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower doses.

Method of Administration

For oral administration.

4.3 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 .
- A catecholamine-secreting tumour such as pheochromocytoma or paraganglioma;

- Depression;
- Therapy with monoamine oxidase inhibitors (MAOIs)
- Porphyria.

4.4 Special warnings and precautions for use

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.

Some patients on continued therapy with methyldopa develop a positive Coombs test. From the reports of different investigators, the incidence averages between 10% and 20%. A positive Coombs test rarely develops in the first six months of therapy, and if it has not developed within twelve months, it is unlikely to do so later on continuing therapy. Development is also dose-related, the lowest incidence occurring in patients receiving 1g or less of methyldopa per day. The test becomes negative usually within weeks or months of stopping methyldopa.

Prior knowledge of a positive Coombs reaction will aid in evaluating a cross-match for transfusion. If a patient with a positive Coombs reaction shows an incompatible minor cross-match, an indirect Coombs test should be performed. If this is negative, transfusion with blood compatible in the major cross-match may be carried out. If positive, the advisability of transfusion should be determined by a haematologist.

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, may also occur. Its onset is usually within the first two or three months of therapy. In some patients the findings are consistent with those of cholestasis. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy, performed in several patients with liver dysfunction, showed a microscopic focal necrosis compatible with drug hypersensitivity. Liver function tests and a total and differential white blood cell count are advisable before therapy and at intervals

during the first six weeks to twelve weeks of therapy, or whenever an unexplained fever occurs.

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.

This medicine contains sunset yellow (E110) which may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially

'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interact.

Alcohol: concomitant use may enhance the hypotensive effect.

Alprostadil: concomitant use may enhance the hypotensive effect.

Anaesthetics: as concomitant use may enhance the hypotensive effect, patients may require reduced doses of anaesthetics when on methyldopa. If hypotension does occur during anaesthesia, it can usually be controlled by vasopressors.

Antidepressants: concomitant use may enhance the hypotensive effect. Concomitant use with MAOIs should be avoided.

Antihypertensives: 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.

Antipsychotics: concomitant use can increase the risk of extrapyramidal effects and enhance the hypotensive effect. In addition, phenothiazines may have additive hypotensive effects.

Beta-blockers: concomitant use may enhance the hypotensive effect.

Calcium-channel blockers: concomitant use may enhance the hypotensive effect.

Diuretics: concomitant use may enhance the hypotensive effect.

Dopaminergics: concomitant use may antagonise the antiparkinsonian effect of this type of medicine. Concomitant use with levodopa or entacapone may enhance the hypotensive effect.

Iron: concomitant use may reduce the hypotensive effect. Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulfate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa.

Lithium: when methyldopa and lithium are given concomitantly the patient should be monitored carefully for symptoms of lithium toxicity. Neurotoxicity may occur without increased plasma-lithium concentration.

Moxisylyte: concomitant use may enhance the hypotensive effect.

Muscle relaxants: concomitant use with baclofen and tizanidine may enhance the hypotensive effect.

Nitrates: concomitant use may enhance the hypotensive effect.

4.6 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 foetal 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 foetal 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.

4.7 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.

4.8 Undesirable effects

Sedation, usually transient, may occur during the initial period of therapy or when the dose is increased. If affected, patients should not attempt to drive, or operate machinery. Headache, asthenia or weakness may be noted as early and transient symptoms.

The following convention has been utilised for the classification of frequency: Very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

System Organ Class	Adverse event term	Frequency
Infections and infestations	Sialadenitis	Not known
Blood and lymphatic system disorders	Haemolytic anaemia, bone marrow failure, leucopenia, 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, Bell's palsy, 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	Rash (eczema, lichenoid eruption),	Not known

disorders	toxic epidermal necrolysis, angioedema, urticaria	
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 disorders and administration site conditions	Asthenia, oedema (and weight 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

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 EFDA yellow Card Scheme, online at <https://primaryreporting.who-umc.org/ET> or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

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

If ingestion is recent emesis may be induced or gastric lavage performed. There is no specific antidote, but Methyldopa is dialysable.

Treatment is largely symptomatic but if necessary intravenous infusion may be given to promote urinary excretion and pressor agents given cautiously.

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.

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties

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).

5.2 Pharmacokinetic Properties

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.

5.3 Preclinical Safety Data

Not available.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch, Microcrystalline Cellulose, Colloidal Anhydrous Silica, Hypromellose E-15 , Purified Talc, Magnesium Stearate, Stearic acid, Croscarmellose Sodium, Dichloromethane, HypromelloseE-15, Titanium Dioxide, Macrogol 6000, Colour Tartrazine Lake and Isopropyl Alcohol

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

Methyldopa Tablets BP 250 mg is packed in Blister pack.

Pack size: 10 X 10

6.6 Special precautions for disposal

Return any leftover medicine to your pharmacist.

7. MARKETING AUTHORISATION HOLDER

MEDICAMEN Biotech Limited

SP-1192 A&B, PHASE - IV,

Industrial Area, Bhiwadi - 301 019

Distt. Alwar,

Rajasthan, India.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

Registration No; 07961/09021/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION]

Approval date; 21-10-2022

10. DATE OF REVISION OF THE TEXT

July 2024