SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methyldopa Tablets 250mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains methyldopa BP 250mg.

Excipients with known effect

Lecithin (Soy)(E322)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Methyldopa 250mg Tablets are yellow coloured, round, biconvex, film coated tablets plain on both sides with an approximate diameter of 11.6mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension.

4.2 Posology and method of administration

Posology

Adults:

Initial dosage: Usually 250 mg 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 3 g.

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

Paediatric population

Initial dosage is based on 10 mg/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 65 mg/kg or 3.0 g daily, whichever is less.

Elderly

The initial dose in elderly patients should be kept as low as possible, not exceeding 250 mg daily. An appropriate starting dose in the elderly would be 125 mg b.d.

increasing slowly as required, but not to exceed a maximum daily dosage of 2 g. 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 use.

4.3 Contraindications

- hypersensitivity to the active substance (including hepatic disorders associated with previous methyldopa therapy) or to any of the excipients listed in section 6.1
- active hepatic disease, such as acute hepatitis, and active cirrhosis
- depression
- on therapy with monoamine oxidase inhibitors (MAOIs)
- patients with a catecholamine-secreting tumour such as pheochromocytoma or paraganglioma
- porphyria.

Methyldopa Tablets contain lecithin (Soy)(E322), which may contain soya oil. Patients with a hypersensitivity to peanut or soya should not take this medicine.

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 12 months, it is unlikely to do so later on continuing therapy. Development is also dose-related, the lowest incidence occurring in patients receiving 1 g 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 leukopenia, 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 pheochromocytoma or paraganglioma.

It is important to recognise this phenomenon before a patient with a possible pheochromocytoma 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 pheochromocytoma 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 less than 1 mmol sodium (23 mg) per tablet, essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium:

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

Other antihypertensive 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 drug:

The antihypertensive effect of Methyldopa may be diminished by sympathomimetics, phenothiazines, tricyclic antidepressants and MAOIs (see section 4.3). In addition, phenothiazines may have additive hypotensive 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.

4.6 Fertility, 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 whenever 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥ 1/10,000 to <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	Haemolytic anaemia,	Not known

system disorders	bone marrow failure, leukopenia, granulocytopenia, thrombocytopenia, eosinophilia	
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,	Not known

	pancreatitis	
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 disorders and administration side 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 the Yellow Card Scheme at:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Acute overdosage 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 tablets should be discontinued.

5 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-methylnoradrenaline, 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

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium calcium edetate, citric acid, sodium starch glycolate, microcrystalline cellulose, ethyl cellulose, colloidal anhydrous silica and magnesium stearate.

Film coating: polyvinyl alcohol (E1203), purified talc (E553b), iron oxide yellow (E172), titanium dioxide (E171), lecithin (Soy)(E322) and Xanthan gum (E415).

6.2 Incompatibilities

See Section 4.5, “Interactions with other medicaments and other forms of interaction”.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Securitainers.

Pack size: 56 Tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd,
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UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0045

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10 DATE OF REVISION OF THE TEXT

23/08/2023