SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Methyldopa 250 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:
This product contain 1,5 mg glycerol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1Therapeutic indications

Methyldopa is indicated for the treatment of hypertension.

4.2 Posology and method of administration

Posology

Adults
The initial dose of Methyldopa is usually 250 mg two to three times daily for two days. The dose may be adjusted at intervals of not less than two days until adequate response is achieved. 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 or hepatic impairment
Methyldopa is mainly excreted by the kidneys therefore patients with renal dysfunction may respond well to lower doses.

Other antihypertensives
Therapy with Methyldopa may be initiated in most patients already on treatment with otherantihypertensive 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 has to be adjusted to effect a smooth transition.

When 500 mg of Methyldopa is added to 50 mg or 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 g daily, whichever is less.

Older people
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
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 listed in section 6.1.
- depression.
- on therapy with monoamine oxidase inhibitors (MAOIs).
- with a catecholamine-secreting tumour such as phaeochromocytoma or paraganglioma.
- with 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 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 hematologist.

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. 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.

4.5 Interaction with other medicinal productsand other forms of interaction

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

Other 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 4.3 '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.

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 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.

Lactation
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, may occur 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 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 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	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,	Not known

	colitis, dry mouth, glossodynia, tongue discolouration, 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 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

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 national reporting system.

4.9 Overdose

Symptoms

Acute overdosage with Methyldopa may produce acute hypotension with other responses attribute 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives, Antiadrenergic agents, centrally acting,
ATC code: C02AB02

Mechanism of action
It appears that several mechanisms of action account for the clinically useful effects of methyldopa exist 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 metabolismto 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

No relevant information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Povidone
Glycerol
Cellulose microcrystalline
Magnesium stearate
Silica colloidal anhydrous
Disodium edetate
Citric acid
Talc

Coating
Hypromellose
Macrogol 400
Titanium dioxide
Ferric oxide yellow E172
Talc

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25˚C.Protect from light and moisture.

6.5 Nature and contents of container

PVC / PVDC – Aluminium blisters. Pack-sizes of 30,100and 1000 film-coatedtablets.
PP containers with PE closure. Pack-size of 1000 film-coated tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

06269/07920/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OFTHE AUTHORISATION

Date of latest renewal: Dec 28, 2021

10. DATE OF REVISION OF THE TEXT

04/07/2023