1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

(ALMET TABLETS) Methyldopa Tablets 250mg

2. Qualitative and quantitative composition

Each tablet contains 250 mg Methyldopa.

3. Pharmaceutical form

Round, yellow film coated biconvex tablet

4. Clinical particulars

4.1 Therapeutic indications

Treatment of moderate to severe hypertension

4.2 Posology and method of administration

Posology

Since Methyldopa is largely excreted by the kidneys, patients with impaired renal function may respond to comparatively low doses.

Withdrawal of Methyldopa which is followed by return of hypertension, usually within 48 hours, is not complicated generally by an overshoot of blood pressure.

Therapy with Methyldopa may be initiated in most patients already on treatment with other antihypertensive agents by terminating these antihypertensive medications gradually if required (see manufacturer's recommendations on stopping these drugs). 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.

A thiazide may be added at any time during Methyldopa therapy and is recommended if therapy has not been started with a thiazide or if effective control of blood pressure cannot be maintained on 2g of Methyldopa daily.

Methyldopa may also be used concomitantly with the combination of amiloride hydrochloride and hydrochlorothiazide or beta-blocking agents, such as timolol maleate.

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

Adults and children over 12 years: Initially 250mg two or three times a day, for two days. Thereafter, usually increased at intervals of not less than two days until an adequate response is achieved. The maximum recommended daily dose should not exceed 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.

Children under 12 years: Initial dosage is based on 10mg/kg of bodyweight daily in 2-4 divided doses increased or decreased as required. The maximum dose is 65mg/kg or 3g daily, whichever is less.

Elderly: The initial dose should be kept as low as possible, not exceeding 250mg daily. An appropriate starting dose would be 125mg twice daily increasing slowly as required, to a maximum of 2g daily. An alternative tablet preparation may therefore be required initially for this age group.

Method of Administration

For oral administration.

4.3 Contraindications

- Active hepatic disease (such as acute hepatitis and active cirrhosis);
- Hypersensitivity (including hepatic disorders associated with previous methyldopa therapy) to methyldopa or any of the ingredients in the tablets;
- Phaeochromocytoma;
- Depression;
- Therapy with monoamine oxidase inhibitors (MAOIs).

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 tablets 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 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.

Methyldopa Tablets should be used with extreme caution in patients, or in near relatives of patients, with hepatic porphyria.

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 phaeochromocytoma or paraganglioma.

It is important to recognise this phenomenon before a patient with a possible phaeochromocytoma or paraganglioma 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.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.
Analgesics: NSAIDs antagonise the hypotensive effect.
Antibacterials: concomitant use with linezolid should be avoided as the hypotensive effect may be enhanced.
Antidepressants: concomitant use may enhance the hypotensive effect. Concomitant use with MAOIs should be avoided.
Antihypertensives: the use of other antihypertensives may enhance the hypotensive effect. The progress of patients should be carefully monitored to detect side-effects or manifestations of drug idiosyncrasy.
Antipsychotics: concomitant use can increase the risk of extrapyrimidal effects and enhance the hypotensive effect.
Anxiolytics and hypnotics: concomitant use may enhance the hypotensive effect.
Beta-blockers: concomitant use may enhance the hypotensive effect.
Calcium-channel blockers: concomitant use may enhance the hypotensive effect.
Corticosteroids: concomitant use may antagonise 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 sulphate 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.
Oestrogens and progestogens: oestrogens and combined oral contraceptives antagonise the hypotensive effect.
Beta2 sympathomimetics: acute hypotension has been reported with salbutamol infusion.
Ulcer-healing drugs: carbenoxolone antagonises the hypotensive effect.
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 the colorimetric method. Interference of the latter with spectrophotometric methods have 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 phaeochromocytoma.
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.
Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites.

4.6 Fertility, pregnancy and lactation

Pregnancy

Methyldopa has been used under close medical supervision for the treatment of hypertension during pregnancy. There is no clinical evidence of foetal abnormalities or effect on 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.

Breast-feeding

Methyldopa crosses the placental barrier and is present in cord blood and appears in breast milk. 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 or who are breast-feeding their newborn infant requires that anticipated benefits be weighed against possible risks.

4.7 Effects on ability to drive and use machines

Caution should be observed when driving or operating machinery, as methyldopa therapy may result in drowsiness, dizziness, light headedness, involuntary choreoathetotic movements in patients with severe cerebrovascular disease. The patient should be advised accordingly on initiation of therapy and/or increase in dosage.

4.8 Undesirable effects

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**
Cardiac disorders	Bradycardia, aggravation of angina pectoris,	Not known

	myocarditis, pericarditis, atrioventricular block	
Blood and lymphaticsystem disorders	Haemolytic anaemia, bone-marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia	Not known
Nervous system disorders	Sedation (usually transient)*, headache**, paraesthesia, Parkinsonism, VIIth nerve paralysis, choreoathetosis*, mental impairment, carotid sinus syndrome, dizziness*, light-headedness*, symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)	Not known
Respiratory, thoracic andmediastinal disorders	Nasal Stuffiness	Not known
Gastrointest inal disorders	Nausea, vomiting, abdominal distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or 'black' tongue, pancreatitis	Not known
Skin and subcutaneoustissue disorders	Rash as in eczema or lichenoid eruption, toxic epidermal necrolysis, angioedema, urticaria	Not known
Musculoskeletal andconnective tissue disorders	Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia	Not known
Endocrine disorders	Hyperprolactinaemia	Not known
Infections and Infestation s	Sialadentis	Not known
Vascular disorders	Orthostatic hypotension (decrease daily dosage)	Not known
General disorders andadministrative site conditions	Asthenia or weakness**, oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear.), drug-related fever	Not known
Hepatobiliary disorders	Liver disorders including hepatitis, jaundice	Not known
Reproductive system andbreast disorders	Breast enlargement, gynaecomastia, amenorrhoea, lactation, impotence, failure of ejaculation	Not known
Psychiatric disorders	Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido	Not known

Investigations	Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, rise in blood urea	Not known

*Sedation, usually transient, may occur during the initial period of therapy or whenever the doseis increased. If affected, patients should not attempt to drive, or operate machinery.

**Headache, asthenia or weakness may be noted as early and transient symptoms.

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. Pharmacological properties

5.1 Pharmacodynamic properties

Methyldopa is an antihypertensive agent acting centrally by stimulating alpha adrenergic receptors. It inhibits the decarboxylation of dopa to dopamine but this action is not responsible for the hypotensive effect. It is suggested that a metabolite, alpha methylnoradrenaline may act as a false transmitter in the CNS. It reduces tissue concentration of dopamine noradrenaline, adrenaline and serotonin.

5.2 Pharmacokinetic properties

Methyldopa is incompletely absorbed from the gastrointestinal tract. Methyldopa is extensively metabolised through pathways common to the catecholamines utilising dopa decarboxylates and dopamine B-hydroxylase.

Decarboxylation is stereospecific. The bioavailability of an oral dose averages 25%(± 16%) and peak plasma levels occur 2 to 3 hours later. Elimination is biphasic. It is partly conjugated mainly to the o-sulphate and is excreted by the kidneys.

The elimination half-life is 1.8 ± 0.2 hours, methyldopa has been shown to cross the placental barrier and is found in the lungs, heart and muscles after 24 hours, detectable quantities are present in the liver and kidneys.

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

Dextrin
Corn starch
Hydroxypropyl cellulose
Sodium bisulfite
Vitamin C
Hydroxypropyl methyl cellulose (Hypromellose)
Alcohol
Magnesium stearate
Sodium starch glycolate
Film coating material

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Pack sizes: 10*10's/box, 10box/seal, 200boxes/carton

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

REAGAN REMEDIES LTD

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