SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methyldopa 500 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Methyldopa equivalent to 500mg anhydrous methyldopa.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Appearance: Yellow, circular, normal convex, film-coated tablets embossed PV on one side and MD/500 on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In the treatment of mild, moderate or severe hypertension

4.2 Posology and Method of Administration

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

Withdrawal of methyldopa is followed by return of hypertension, usually within 48 hours. This 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, 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 500mg of methyldopa is added to 50mg or hydrochlorothiazide, the two agents may be given together once daily.

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.

**Adults:**

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

**Adjustment:** Usually adjusted by amounts of 250 mg a day, at intervals of not less than two days, until an adequate response is obtained. The maximum recommended daily dose is 3 g.

**Children:** Initial dosage is based on 10 mg/kg of body weight daily in 2 to 4 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.

**Use in the 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 exceeding 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.

### 4.3 Contra-indications

Depression, active hepatic disease such as acute hepatitis and active cirrhosis.

Hypersensitivity to any of the ingredients (including hepatic disorders associated with previous methyldopa therapy), porphyria.

On therapy with monoamine oxidase inhibitors (MAOIs).

Methyldopa is not recommended for the treatment of phaeochromocytoma (see special warnings and precautions for use).
4.4 Special warnings and precautions for use

Acquired haemolytic anaemia has occurred rarely in association with methyldopa therapy. 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 direct 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 usually becomes negative within weeks or months of stopping methyldopa.

Prior knowledge of a positive Coombs reaction will help 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.

On rare occasions, a reduction of the white cell count with a primary effect on the granulocytes has been seen. The granulocyte count promptly returned to normal when methyldopa was discontinued. 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 at intervals during the first six weeks to twelve weeks of therapy, regularly during long-term treatment, or whenever an unexplained fever occurs.

Should fever, abnormality in liver function, or jaundice occurs, 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 liver disease or dysfunction.
The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy. Tolerance to this product may occur. A paradoxical pressor response has been reported with methyldopa injection.

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.

If cerebral or myocardial infarction occurs during therapy with methyldopa adjustment of dosage or temporary cessation of methyldopa may be required during the acute phase. Therapy with methyldopa should not be initiated during the acute phase of cerebral or myocardial infarction.

Rarely, involuntary choreo-athetotic movements have been observed during therapy with methyldopa in patients with severe bilateral cerebrovascular disease. Should these movements occur, therapy should be discontinued.

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

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

Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower doses (see posology and method of administration).

*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.

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

When methyldopa is given concomitantly with lithium and haloperidol the patient should be monitored carefully for symptoms of toxicity. Neurotoxicity may occur without increased plasma concentrations of lithium.

When methyldopa is used with other antihypertensive drugs (alpha-blockers, adrenergic neurone blockers, angiotensin II receptor antagonists, nitrates, beta-blockers, diuretics, calcium-channel blockers, clonidine, hydralazine) or alcohol, the anti-hypertensive action may be enhanced. The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy.

Similarly, the antihypertensive effect may be modified by concurrent administration of tricyclic antidepressants, sympathomimetics, aldesleukin, tizanidine, alprostadil, moxonidine, anaesthetics, anti-psychotics, anxiolytics, hypnotics, baclofen, moxisylyte, levodopa, diazoxide, phenothiazines and MAOIs. Hypotensive effects of methyldopa antagonised by corticosteroids, oestrogen, iron, and NSAIDS.

Acute hypertension is reported when methyldopa given with infusion of salbutamol.

Increased risk of extrapyramidal side effects when methyldopa given with amantadine

Methyldopa antagonises antiparkinsonian effect of dopaminergic.

Several studies have demonstrated 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 Pregnancy and Lactation

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 and 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 nursing their newborn infants requires that anticipated benefits be weighed against possible risks.

4.7. Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Significant side effects, due to methyldopa have been infrequent and this agent is usually well tolerated. The following reactions have been reported:

Nervous system disorders: Sedation (usually transient), headache, parasthesiae, Parkinsonism, Bell’s palsy, involuntary choreoathetotic movements. Dizziness, light-headedness, and symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure). Headache, asthenia or weakness may be noted as early and transient symptoms.

Cardiac disorders: Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris, myocarditis, pericarditis. Oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear).

Gastro-intestinal disorders: Nausea, vomiting, distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or “black” tongue, pancreatitis, sialadenitis.

Hepatobiliary disorders: Liver disorders including hepatitis, jaundice and abnormal liver-function tests.

Blood and lymphatic system disorders: Haemolytic anaemia, bone marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor.

Musculoskeletal and connective tissue disorders: Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia.

Skin and subcutaneous tissue disorders: Rash as in eczema or lichenoid eruption, toxic epidermal necrolysis.

Endocrine disorders: Hyperprolactinaemia

Infectious and infestations: Sialadentis

Vascular disorders: Orthostatic hypotension (decrease daily dosage).
General disorders and administrative site conditions: Asthenia or weakness, oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs or heart failure appear.), nasal stuffiness, drug-related fever.

Reproductive system and breast disorders: Breast enlargement, gynaecomastia, amenorrhoea, lactation, impotence, failure of ejaculation.

Psychiatric disorders: Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido.

Investigations: Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, rise in blood urea.

4.9 Overdose

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

If ingestion is recent, emesis may be induced or gastric lavage performed. There is no specific antidote. 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 e.g. noradrenaline may be indicated. When chronic overdosage is suspected, methyldopa should be discontinued.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Methyldopa is thought to exert its hypotensive effect within the central nervous system (CNS) by virtue of its conversion to α-methylnorepinephrine, a potent α2-adrenergic agonist. By analogy with the actions of clonidine, this would lead to a decrease in sympathetic outflow from the CNS. This hypothesis is supported by the following observations. Inhibition of the decarboxylation of methyldopa centrally, but not in the periphery, blocks the hypotensive effect of the drug. Pre-treatment with phentolamine also blocks methyldopa’s hypotensive effect. Furthermore, the effects of methyldopa on blood pressure do not correlate with reductions in the concentration of
norepinephrine in the CNS. While additional central or peripheral mechanisms cannot be ruled out, they probably play only a minor role.

5.2. Pharmacokinetic properties

Absorption of oral methyldopa is variable and incomplete. Bioavailability after oral administration averages 25%. Peak concentrations in plasma occur at 2 to 3 hours, and elimination of the drug is biphasic regardless of the route of administration. Renal excretion accounts for about two thirds of drug clearance from plasma. Slow elimination of unidentified active metabolites occurs in patients with renal failure, and dosage should be reduced in patients with hepatic or renal dysfunction; the hypotensive response should also be titrated carefully.

5.3. Preclinical safety data

No information submitted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, povidone, sodium starch glycollate, magnesium stearate.

Film coat: Hypromellose, propylene glycol, titanium dioxide (E171), polyethylene glycol, quinoline yellow aluminium lake (E104), iron oxide yellow (E172), sunset yellow aluminium lake (E110).

6.2. Incompatibilities

None stated.

6.3. Shelf life

3 years.
6.4. Special precautions for storage

Do not store above 25°C.
Store in the original container to protect from light.
Keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene securitainer with high density polyethylene cap. Silica gel sachet is enclosed.

Pack sizes 7, 14, 28, 56, 84, 100, 500, 1000.

6.6. Instructions for use and handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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