1. NAME OF MEDICINAL PRODUCT

Aldomet 250 mg (tablets)
Aldomet 500 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aldomet 250 mg: Each tablet contains 250 mg methyldopa.
Aldomet 500 mg: Each tablet contains 500 mg methyldopa.

3. PHARMACEUTICAL FORM

Aldomet 250 mg tablets are round, biconvex, yellow film coated tablets marked with "ALDOMET" on one side and "250" on the other side.
Aldomet 500 mg tablets are round, biconvex, yellow film coated tablets marked with "ALDOMET" on one side and "500" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of 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 500 mg of methyldopa is added to 50 mg of 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 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.

Children

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.

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 twice per day. 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.

4.3 Contraindications

Methyldopa is contraindicated in patients with:

- hypersensitivity (including hepatic disorders associated with previous methyldopa therapy) to any component of these products
- active hepatic disease, such as acute hepatitis and active cirrhosis
- depression
- 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; 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 doserelated, 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 crossmatch 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 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.

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

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 Contraindications'). 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 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.

Lactation

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 breast-feeding their newborn infant 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

Adverse reactions that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common (1/100 to <1/10); uncommon (1/1,000 to <1/100); rare (1/10,000 to <1/1,000); very rare (<1/10,000) and not known (frequency cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

The following reactions have been reported:

Infections and infestations

Not known: Sialadenitis

Blood and lymphatic system disorders

Not known: Haemolytic anaemia, bone-marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia

Endocrine disorders

Not known: Hyperprolactinaemia

Psychiatric disorders

Not known: Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido.

Nervous system disorders

Common: Sedation (usually transient), headache, dizziness,

Not known: Paraesthesia, Parkinsonism, Bell's palsy, involuntary choreoathetotic movements. Impaired mental acuity, prolonged carotid sinus hypersensitivity, light-headedness, and symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)

Cardiac disorders

Not known: Bradycardia, aggravation of angina pectoris, myocarditis, pericarditis

Vascular disorders

Not known: Orthostatic hypotension (decrease daily dosage)

Respiratory, thoracic and mediastinal disorders

Not known: Nasal stuffiness

Gastrointestinal disorders

Not known: Nausea, vomiting, distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or 'black' tongue, pancreatitis

Hepatobiliary disorders

Not known: Liver disorders including hepatitis, jaundice

Skin and subcutaneous tissue disorders

Not known: Rash as in eczema or lichenoid eruption, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Not known: Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia

Reproductive system and breast disorders

Common: Impotence, failure of ejaculation, reduced libido

Not known: Breast enlargement, gynaecomastia, amenorrhoea, lactation

General disorders and administrative site conditions

Common: Asthenia or weakness, drug-related fever.

Not known: Oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear.)

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

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).

Treatment

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

Pharmacotherapeutic group: A 7.1.3 Other hypotensives.

ATC Code: C02AB

5.1 Pharmacodynamic properties

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 %. Peak concentrations in plasma occur at

two to three hours.

Elimination

Elimination of methyldopa is biphasic regardless of the route of administration. Plasma half-life is 1,8 ± 0,2 hours. 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

Methyldopa 250 mg:
Ethylcellulose,
Citric Acid Anhydrous,
Edetate Calcium Disodium,
Guar Gum,
Colloidal Silicon Dioxide,
Powdered Cellulose,
Magnesium Stearate,

Tablet coat
Opadry 03H38061 Yellow,
Carnauba Wax powder

Methyldopa 500 mg
Eethylcellulose,
Citric Acid Anhydrous
Sodium Calcium Edetate
Jaguar Gum A-20-B (guar gum);
Colloidal Silicon Dioxide;
Powdered cellulose,
Magnesium Stearate

Tablet coat
Opadry Yellow 03H38061;
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Country specific

Store at or below 25°C.
Protect From light.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Aldomet 250 mg: Opaque 250 micron PVC/20 micron aluminium blisters. Each pack contains 30 tablets.

Aldomet 500 mg: Opaque 250 micron PVC/20 micron aluminium blisters. Each pack contains 30 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKET AUTHORISATION HOLDER

Aspen Global Incorporated
GBS Plaza
Cnr la salette and royal roads
Grand-Bay
Mauritius

OR

Information of MAH within territory where SPC will be submitted

References:

1.	UK/EMEA SPC. Methyldopa 500 mg tablets. Last updated 18/12/2013
2	SA PI .Hy-po-tone 250 and 500 mg Tablets. Date of publication of package insert: 12 March 2013.
3.	Methyldopa Micromedex on line access_12/08/2014.