Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aldomet Film-coated Tablets 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

'Aldomet' tablets 500mg, contain methyldopa equivalent to 500mg anhydrous methyldopa.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets
Yellow coloured, round, film-coated tablets marked 'ALDOMET' on one side and '500' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of hypertension (mild, moderate or severe).

4.2 Posology and method of administration

Posology

Use in 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 'Aldomet' 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 'Aldomet' 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 'Aldomet' 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, 'Aldomet ' 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.

'Aldomet' may also be used concomitantly with the combination of amiloride hydrochloride and hydrochlorothiazide (such as Moduret-25) 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.

Paediatric population:
Initial dosage is based on 10 mg/kg of bodyweight daily in 2 to 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:
Syncope in the older patient may be related to an increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by using lower doses.

Method of administration
Oral.

4.3 Contraindications

'Aldomet' is contra-indicated in patients:

- with active hepatic disease, such as acute hepatitis and active cirrhosis
- with hypersensitivity to the active substance (including hepatic disorders associated with previous methyldopa therapy), or to any of the excipients listed in section 6.1
- with 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, 'Aldomet' 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, 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.

Tolerance to this product may occur.

Dialysis removes methyldopa: therefore, hypertension may recur after this procedure.

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

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 not recommended for the treatment of patients with phaeochromocytoma.

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 used with other antihypertensive drugs or alcohol, the antihypertensive action may be enhanced.

Similarly the antihypertensive effect may be modified by concurrent administration of tricyclic antidepressants, sympathomimetics, phenothiazines and monoamine oxidase inhibitors (MAOIs).

Interaction with haloperidol has been reported.

When methyldopa and lithium are given concomitantly the patient should be monitored carefully for symptoms of lithium toxicity. The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy.

Several studies demonstrate a decrease in 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
'Aldomet' has been used under close medical supervision for the treatment of hypertension during pregnancy. There was no clinical evidence that 'Aldomet' caused foetal abnormalities or affected the neonate.

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

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

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, colitis, dry mouth, glossodynia, tongue discolouration, pancreatitis	Not known
Hepatobiliary disorders	Liver disorders including hepatitis, jaundice	Not known
Skin and subcutaneous tissue disorders	Rash (eczema, lichenoid eruption), toxic epidermal necrolysis	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 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; HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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, ‘Aldomet’ should be discontinued.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiadrenergic agents; ATC code C02AB

Mechanism of action
Methyldopa reduces both supine and standing blood pressure. It usually produces highly effective lowering of the supine pressure with infrequent symptomatic postural hypotension. Exercise hypotension and diurnal blood pressure variations rarely occur.

Pharmacodynamic effects
The maximum decrease in blood pressure occurs four to six hours after oral dosage. Once an effective dosage level is attained, a smooth blood-pressure response occurs in most patients in 12 to 24 hours. After withdrawal, blood pressure usually returns to pre-treatment levels within 24 to 48 hours.

Methyldopa has no direct effect on cardiac function and usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction, cardiac output usually is maintained without cardiac acceleration. In some patients the heart rate is slowed.

Normal or elevated plasma renin activity may decrease in the course of methyldopa therapy.

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. Plasma half-life is 1.8 ± 0.2 hours.

Elimination
Approximately 70% of the oral form of the drug which is absorbed is excreted in the urine as methyldopa and its mono-O-sulphate conjugate.

Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

5.3 Preclinical safety data

No relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Cellulose powder
Anhydrous citric acid
Colloidal anhydrous silica
Ethylcellulose

Guar gum
Magnesium stearate
Sodium calcium edetate

Tablet Coating

Propylene glycol
Anhydrous citric acid
Hypromellose
Quinoline yellow aluminium lake (E104)
Red iron oxide (E172)
Talc
Titanium dioxide
Carnauba Wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Bottle

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

Blister

Do not store above 25°C
Store in the original package in order to protect from light.

6.5 Nature and contents of container

White polyethylene bottle of 100 and 500 tablets with turquoise polyethylene closure. PVC blister packs with aluminium lids contain 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/012/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 April 1979

Date of last renewal: 1 April 2009

10 DATE OF REVISION OF THE TEXT

August 2016