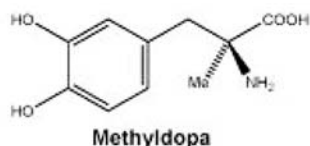


## PRODUCT INFORMATION

### **ALDOMET<sup>®</sup>** 250mg Tablets (methyldopa)

#### NAME OF THE MEDICINE

Methyldopa is the L-isomer of alpha-methyldopa. Chemical name: (-)-3-(3,4-dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate. Molecular formula:  $C_{10}H_{13}NO_4 \cdot 1\frac{1}{2}H_2O$ . MW: 238.2. CAS: 41372-08-1.



#### DESCRIPTION

Methyldopa is a white to yellowish white crystalline powder or almost colourless crystals. It is odourless and almost tasteless. It is slightly soluble in water and in ethanol (96%), and is practically insoluble in ether and in chloroform. It dissolves in dilute mineral acids.

Excipients: Anhydrous citric acid, sodium calcium edetate, ethylcellulose, hypromellose, guar gum, anhydrous colloidal silica, magnesium stearate, propylene glycol, ethylcellulose, talc, titanium dioxide, cellulose, iron oxide red CI77491 and quinoline yellow CI47005.

#### PHARMACOLOGY

ALDOMET<sup>®</sup> (methyldopa) is an effective anti-hypertensive agent that reduces both supine and standing blood pressure. Symptomatic postural hypotension, exercise hypotension and diurnal blood pressure variations rarely occur. By adjustment of dosage, morning hypotension can be prevented without sacrificing control of afternoon blood pressure.

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.

Because of relative freedom from adverse effects on kidney function, methyldopa can be of benefit in the control of high blood pressure, even in the presence of renal impairment. It may help arrest or retard the progression of renal function impairment and damage due to sustained elevation of blood pressure.

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

The ability to inhibit dopa decarboxylase and to deplete animal tissue of noradrenaline resides solely in the L-isomer (methyldopa). In man, the antihypertensive activity appears to be due solely to the L-isomer.

#### INDICATION

Hypertension (mild, moderate to severe).

## CONTRAINDICATIONS

ALDOMET is contraindicated in patients:

- with active hepatic disease, such as acute hepatitis and active cirrhosis.
- with hypersensitivity (including hepatic disorders associated with previous methyldopa therapy) to any component of these products. (See PRECAUTIONS).
- on therapy with monoamine oxidase(MAO)inhibitors.

## PRECAUTIONS

### Anaemia

Acquired haemolytic anaemia has occurred rarely in association with methyldopa therapy. Should clinical symptoms indicate the possibility of anaemia, haemoglobin and/or haematocrit determinations should be performed. If anaemia is present, appropriate laboratory studies should be done to determine if haemolysis is present. Evidence of haemolytic anaemia is an indication for discontinuation of the drug. Discontinuation of methyldopa alone, or the initiation of adrenocortical steroids, usually results in a prompt remission of anaemia. Rarely, however, fatalities have occurred.

### Coombs Test

Some patients on continued therapy with methyldopa develop a positive direct Coombs test. The incidence of positive Coombs test as reported by different investigators has averaged between 10 and 20 percent. A positive Coombs test rarely occurs in the first six months of therapy with methyldopa and if not encountered within 12 months, is unlikely to develop with continued administration. This phenomenon is also dose-related with the lowest incidence occurring in patients receiving 1g of methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of the drug.

Should the need for transfusion arise, prior knowledge of a positive Coombs reaction will aid in evaluation of the cross match. Patients with a positive Coombs test at the time of cross match may exhibit an incompatible minor cross match. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with such blood which is otherwise compatible in the major cross match may be carried out. However, if positive, the advisability of transfusion with blood compatible in the major cross match should be determined by a haematologist or expert in transfusion problems.

Rarely, a reversible reduction of the white blood cell count with a primary effect on the granulocytes has been seen. The granulocyte count returned promptly to normal on discontinuance of the drug. Reversible thrombocytopenia has occurred rarely.

### Fever and Hepatic Function

Occasionally, fever has occurred within the first three weeks of administration of methyldopa. In some cases this fever has been associated with eosinophilia or abnormalities in one of more liver function tests. Jaundice, with or without fever, may occur also, with onset 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. A determination of hepatic function and a white cell and differential blood count should be done at intervals during the first 6 - 12 weeks of therapy, or whenever an unexplained fever may occur. If fever, abnormalities in liver function tests, or jaundice appear, therapy with methyldopa should be stopped. If related to methyldopa, the temperature and abnormalities in liver function characteristically

have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such 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 ALDOMET. 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.

#### 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 SGOT by colorimetric method. Interference with spectrophotometric methods for SGOT analysis has not been reported.

Since methyldopa will cause fluorescence in urine samples at the same wave lengths as catecholamines, spuriously high concentrations of urinary catecholamines may be reported. This will interfere with the 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 measurement 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.

#### Use in Pregnancy (Category A)

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

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

Methyldopa does cross 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.

#### Use in Lactation

Methyldopa appears in breast milk. Therefore, caution should be exercised if ALDOMET is given to a breast feeding mother.

#### Drug Interactions

##### *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 in combination with other antihypertensive drugs, potentiation of antihypertensive action may occur. Patients should be followed carefully to detect adverse reactions or unusual manifestations of drug idiosyncrasy.

### *Iron*

Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulfate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa.

### *Monoamine Oxidase(MAO)Inhibitors*

See CONTRAINDICATIONS.

## **ADVERSE REACTIONS**

Sedation, usually transient, may occur during the initial period of therapy, or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

Significant adverse effects due to ALDOMET have been infrequent and this agent is usually well tolerated.

The following reactions have been reported:

### Central Nervous System

Sedation (usually transient), headache, asthenia or weakness, paraesthesias, parkinsonism, Bell's palsy, involuntary choreoathetotic movements. Psychic disturbances, including nightmares, impaired mental acuity and reversible mild psychoses or depression. Dizziness, light-headedness and symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure).

### Cardiovascular

Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Oedema (and weight gain) usually relieved by use of a diuretic (discontinue methyldopa if oedema progresses or signs of heart failure appear).

### Gastrointestinal

Nausea, vomiting, distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or 'black' tongue, pancreatitis, sialoadenitis.

### Hepatic

Liver disorders including hepatitis, jaundice, abnormal liver function tests.

### Haematological

Positive Coombs test, haemolytic anaemia, bone marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor.

### Allergic

Drug-related fever and abnormal liver function tests with jaundice and hepatocellular damage (see PRECAUTIONS), lupus-like syndrome, myocarditis, pericarditis.

### Dermatological

Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis.

Other

Nasal stuffiness, rise in BUN, breast enlargement, gynaecomastia, lactation, hyperprolactinaemia, amenorrhoea, impotence, decreased libido, mild arthralgia, with or without joint swellings, myalgia.

**DOSAGE AND ADMINISTRATION**General

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.

Withdrawal of ALDOMET is followed by return of hypertension, usually within 48 hours. This is not complicated by an overshoot of blood pressure.

Therapy with ALDOMET may be initiated in most patients already on treatment with other antihypertensive agents.

ALDOMET may also be used concomitantly with MODURETIC® or beta-blocking agents. Many patients can be controlled with one tablet of MODURETIC and 500mg of ALDOMET administered once daily.

When methyldopa is given to patients on other antihypertensives, the dose of these agents may need to be adjusted to effect a smooth transition. Terminate these antihypertensive medications gradually if required (see manufacturers' recommendations on stopping these drugs).

Following such previous antihypertensive therapy, the initial dose of ALDOMET should be limited to not more than 500mg daily and increased as required at intervals of not less than 2 days.

Adults

The usual starting dose of ALDOMET is 250mg two or three times a day in the first 48 hours. The daily dosage may then be increased or decreased, preferably at intervals of not less than two days, until an adequate response is achieved. The maximum recommended daily dosage is 3g.

When ALDOMET 500mg is added to 50mg of hydrochlorothiazide, the two agents may be given together once daily.

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.

Children

Initial dosage is based on 10mg/kg of body weight daily in two to four doses. The daily dosage is then increased, or decreased, until an adequate response is achieved. The maximum dosage is 65mg/kg or 3.0g daily, whichever is less.

**PRESENTATION**

ALDOMET® 250mg, yellow, biconvex, circular shaped tablet, film coated. "250" on one side and "ALDOMET" on the other. Supplied in bottles of 100.

**STORAGE CONDITIONS**

Store below 30°C

**NAME AND ADDRESS OF SPONSOR**

Aspen Pharmacare Australia Pty Ltd  
34-36 Chandos St  
St Leonards NSW 2065

**POISON SCHEDULE S4**

Amendment to Product Information 16 June 1995, 15 September 1999 & 10 December 1999. Safety related changes notified to the Therapeutic Goods Administration on 16 January 1996 and 14 September 1998.

Amendment 22 December 2008.

Amendment 9 March 2009.