NEW ZEALAND DATA SHEET

METHYLDOPA MYLAN

1. Product Name

Methyldopa Mylan, 250 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 250 mg of methyldopa (as anhydrous).

3. Pharmaceutical Form

250 mg tablet: Yellow film coated normal convex tablets, 10.2 mm in diameter, imprinted 'MD' over '250' on one side and 'G' on the other.

4. Clinical Particulars

4.1 Therapeutic indications

Hypertension (mild, moderate or severe).

4.2 Dose and method of administration

Dose

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

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

Methyldopa may also be used concomitantly with amiloride/hydrochlorothiazide tablets or beta-blocking agents, such as timolol maleate. Many patients can be controlled with one tablet of amiloride 5 mg/hydrochlorothiazide 50 mg and 500 mg of methyldopa 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 medicines)

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

Adults

The usual starting dosage of methyldopa is 250 mg two or three times a day in the first 48 hours. The daily dosage then may 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 3 g.

When methyldopa 500 mg 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.

Paediatric

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

4.3 Contraindications

Methyldopa 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 this product (see section 4.4)
- on therapy with monoamine oxidase (MAO) inhibitors
- with depression
- with a catecholamine-secreting tumour such as phaeochromocytoma or paranganglioma
- with porphyria

4.4 Special warnings and precautions for use

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 cessation of methyldopa therapy. 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 1 g of methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of methyldopa.

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 cessation of methyldopa. Reversible thrombocytopenia has occurred rarely.

Fever and hepatic function

Occasionally, fever has occurred within the first 3 weeks of methyldopa treatment. In some cases this fever has been associated with eosinophilia or abnormalities in one or more liver function tests. Jaundice, with or without fever, may also occur, with onset usually within the 2 or 3 months of commencement 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 medicine hypersensitivity.Periodic determination of hepatic function and a white cell and differential blood count should be performed at intervals during the first 6 to12 weeks of therapy, or whenever an unexplained fever may occur. If fever, abnormalities in liver function tests, or jaundice appear, treatment with methyldopa should be ceased. If related to methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the medicine was discontinued. Methyldopa should not be reinstituted in such patients. Caution should be exercised when methyldopa is used 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 usually can be controlled by vasopressors. The adrenergic receptors remain sensitive during treatment with methyldopa.

Hypertension may recur after dialysis as methyldopa is removed by this procedure.

Depression following methyldopa administration has been reported. Care should be taken to monitor for depression, especially in patients with a history of depression.

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 wavelengths as catecholamines, spuriously high concentrations of urinary catecholamines may be reported. This will interfere with the diagnosis of catecholamine-secreting tumour such as phaeochromocytoma or paraganglioma.

It is important to recognise this phenomenon before a patient with a possible catecholamine-secreting tumour is subjected to surgery. Methyldopa does not interfere with measurement of VMA (vanillylmandelic acid) by those methods which convert VMA to vanillin. Methyldopa is contraindicated for the treatment of patients with 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.

4.5 Interaction with other medicines and other forms of interaction

Other antihypertensive medicines

When methyldopa is used in combination with other antihypertensive medicines, potentiation of antihypertensive action may occur. Patients should be monitored carefully for adverse reactions or unusual manifestations of medicine idiosyncrasy.

Lithium

When methyldopa and lithium are administered concomitantly, the patient should be followed carefully for symptoms of lithium toxicity.

Monoamine oxidase (MAO) inhibitors

See section 4.3.

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 Fertility, pregnancy and lactation

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.

Methyldopa has been used under close medical and obstetric supervision for the treatment of hypertension during pregnancy. There was no clinical evidence that methyldopa 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 methyldopa in women who are, or may become pregnant, necessitates that anticipated benefits be weighed against possible risks.

Breast-feeding

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

Fertility

No data available.

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

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 methyldopa 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, atrioventricular block. Orthostatic hypotension (the daily dosage should be reduced). Oedema (and weight gain) usually relieved by use of a diuretic (discontinue methyldopa therapy 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.

Haemotological

Positive Coombs test, haemolytic anaemia, bone-marrow depression, leucopoenia, 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 section 4.4), lupus-like syndrome, myocarditis, pericarditis, angioedema, urticarial.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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, vomiting).

In the event of overdosage, symptomatic and supportive measures should be employed. When ingestion is recent, gastric lavage or emesis may reduce absorption. When ingestion has been earlier, infusions may be helpful to promote urinary excretion. Otherwise, management includes special attention to cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity. Sympathomimetic medicines (e.g. levarterenol, noradrenaline, metaraminol bitartrate) may be indicated. Methyldopa is dialysable.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives, ATC code: C02AB01

Mechanism of action

Methyldopa is an effective antihypertensive agent that decreases 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 decrease glomerular filtration rate, filtration fraction, or renal blood flow. Cardiac output is usually maintained without cardiac acceleration. The heart rate is slowed in some patients.

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 slow the progression of renal function impairment and damage due to sustained elevation of blood pressure.

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

Only methyldopa, the L-isomer of α-methyldopa, has the ability to inhibit dopa decarboxylase and to deplete animal tissue of noradrenaline. In man, the antihypertensive activity of methyldopa appears to be due solely to the L-isomer.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical Particulars

6.1 List of excipients

Ethylcellulose,
Guar gum,
Sodium starch glycollate,
Citric acid,
Disodium edetate,
Colloidal silicon dioxide,
Magnesium stearate,
Opadry yellow (contains sunset yellow FCF, D & C yellow, hypromellose, titanium dioxide and polyethylene glycol).

Methyldopa is gluten and lactose free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years as applicable.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

HDPE bottle with PP cap. Pack sizes of 100 or 500 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

23 April 1981

10. Date of Revision of the Text

16 July 2018	Revised to SmPC format, updated pregnancy and undesirable effects section.