AUSTRALIAN PRODUCT INFORMATION

HYDOPA™

(methyldopa (as sesquihydrate)) tablets

1 NAME OF THE MEDICINE

Methyldopa (as sesquihydrate).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: sulfites and soya bean products.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

HYDOPA 250mg tablet: 10.2 mm normal convex, yellow, film-coated tablet debossed "MD 250" on one side and "G" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension (mild, moderate to severe).

4.2 DOSE AND METHOD OF ADMINISTRATION

General

Methyldopa is primarily excreted by the kidneys. Therefore, patients with impaired renal function may respond to lower doses. Syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by smaller doses.

Cessation of methyldopa therapy 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 commenced in most patients already on treatment with other antihypertensive agents.

Methyldopa may also be given concomitantly with hydrochlorothiazide or beta-blocking agents.

When methyldopa is administered to patients on other antihypertensives, dosage adjustments of these agents may be required to effect a smooth transition. Withdraw these antihypertensive agents gradually if required (see manufacturers' recommendations on discontinuing these drugs).

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

Adults

The usual starting dose is 250 mg two or three times daily in the first 48 hours. The daily dosage may then be increased or reduced, preferably at intervals of not less than 2 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 treatment with methyldopa is initiated, 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 10 mg/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 65 mg/kg or 3 g daily, whichever is less.

4.3 CONTRAINDICATIONS

HYDOPA 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- on therapy with monoamine oxidase (MAO) inhibitors.
- with a catecholamine-secreting tumour such as phaeochromocytoma or paraganglioma.
- 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 treatment 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 decrease in 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 initial three 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 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 drug hypersensitivity. Periodic determination of hepatic function and a white cell and differential blood count should be performed at intervals during the initial 6 to 12 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 drug 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 can usually 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.

Use in Renal Impairment

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on 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 degradation of methyldopa or its metabolites.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Other antihypertensive drugs

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

Lithium

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

Monoamine oxidase (MAO) inhibitors

See Section 4.3 CONTRAINDICATIONS.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Refer to Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy.

Use in Pregnancy

Pregnancy Category: 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 fetus 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.

Use in Lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (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 drug 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.

Haematological

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), 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 Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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, distention, 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 drugs (e.g. levarterenol, noradrenaline, metaraminol bitartrate) may be indicated. Methyldopa is dialyzable.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain citric acid, disodium edetate, ethylcellulose, sodium starch glycollate, guar gum, colloidal anhydrous silica, magnesium stearate and Opadry Yellow OY-8462 (ARTG PI No: 3116).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottles.

Pack sizes: 30, 90, 100 and 500 film coated tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 69482 - HYDOPA methyldopa (as sesquihydrate) 250mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

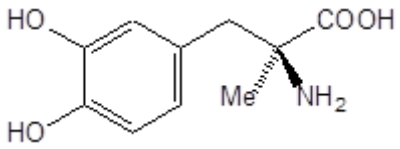
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

Chemical Structure

The active ingredient of HYDOPA is methyldopa, which is the L-isomer of α-methyldopa.



Chemical Name

(-)-3-(3,4-dihydroxyphenyl)-2-methyl-L-alanine

Molecular Formula

C10H13NO4,1½H2O

Molecular Weight

238.2

CAS Number

41372-08-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

10/06/1999

10 DATE OF REVISION

15/08/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2, 6.1	Minor editorial change to update to excipient details
3	Minor editorial change to update match the ARTG details
6.5	Added AUST R details
8	Update to Sponsor details

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