AGOG Pharma Ltd.
(WHO - GMP CERTIFIED - GOVT RECOGNISED EXPORT HOUSE)
Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

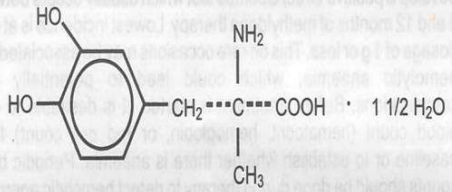
LEAFLET

DOPAMET

(Methyldopa Tablets BP 250 mg)

COMPOSITION :
Each film coated tablet contains:
Methyldopa BP (Anhydrous) .... 250 mg
Excipients ..... q.s.

DESCRIPTION :
Methyldopa is an antihypertensive and is the L-isomer of alpha-methyldopa. It is levo-3-(3,4-dihydroxyphenyl)-2-methylalanine sesquihydrate. Its molecular formula is C10H13NO41 1/2 H2O, with a molecular weight of 238.24, and its structural formula is:



CLINICAL PHARMACOLOGY :
Methyldopa is an aromatic-amino acid decarboxylase inhibitor in animals and in man. The antihypertensive effect of methyldopa probably is due to its metabolism to alpha-methylnorepinephrine, which then 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, norepinephrine, and epinephrine. Only methyldopa, the L-isomer of alpha-methyldopa, has the ability to inhibit dopa decarboxylase and to deplete neither animal tissues of norepinephrine. In man, the antihypertensive activity appears to be due solely to the L-isomer. About twice the dose of the racemate (DL-alpha-methyldopa) is required for equal antihypertensive effect. 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. 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.

PHARMACOKINETICS AND METABOLISM :
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 pretreatment levels within 24–48 hours. Methyldopa is extensively metabolized. Approximately 70 percent of the drug which is absorbed is excreted in the urine as methyldopa and its mono-O-sulfate conjugate. The renal clearance is about 130 ml/min in normal subjects and is diminished in renal insufficiency. The plasma half-life of methyldopa is 105 minutes. After oral doses, excretion is essentially complete in 36 hours. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

INDICATIONS :
It is used in the treatment of Hypertension.

DOSAGE AND ADMINISTRATION :
Use in Adults:
Initiation of Therapy
The usual starting dosage of methyldopa tablet is 250 mg two to 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. To minimize the sedation, start dosage increases in the evening. By adjustment of dosage, morning hypotension may be prevented without sacrificing control of afternoon blood pressure. When methyldopa is given to patients on other antihypertensive, the dose of these agents may need to be adjusted to effect a smooth transition. When methyldopa is given with anti-hypertensive other than thiazides, the initial dosage of methyldopa should be limited to 500 mg daily in divided doses; when methyldopa is added to a thiazides, the dosage of Thiazide need not be changed.

Maintainance of Therapy :
The usual daily dosage of methyldopa is 500 mg to 2 g in two to four doses. Although occasional patients have responded to higher doses, the maximum recommended daily dosage is 3 g. Once an effective dosage range is attained, a smooth blood pressure response occurs in most patients in 12 to 24 hours. Since methyldopa has a relatively short duration of action, withdrawal is followed by return of hypertension usually within 48 hours. This is not complicated by an overshoot of blood pressure. Occasionally tolerance may occur, usually between the second and third month of therapy. Adding a diuretic or increasing the dosage of methyldopa frequently will restore effective control of blood pressure. A Thiazide may be added at any time during methyldopa therapy and is recommended if therapy has not been started with a Thiazide or if effective control of blood pressure cannot be maintained on 2 g of methyldopa daily.

Use in Paediatric :
Initial dosage is based on 10 mg/kg of body weight daily in two to 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 g daily, whichever is less.

Use in Geriatrics :
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

AGOG Pharma Ltd.
(WHO - GMP CERTIFIED - GOVT RECOGNISED EXPORT HOUSE)
Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

1.5.3 Patient information leaflet (PIL)

DRUG INTERACTIONS :
When methyldopa is used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy. Patients may require reduced doses of anesthetics when on methyldopa. If hypotension does occur during anesthesia, it usually can be controlled by vasopressors. The adrenergic receptors remain sensitive during treatment with methyldopa. When methyldopa and lithium are given concomitantly, the patient should be carefully monitored for symptoms of lithium toxicity. There is 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. Coadministration of methyldopa with ferrous sulfate or ferrous gluconate is not recommended.

CONTRAINDICATIONS:
Methyldopa is contraindicated in patients:
1) With active hepatic disease, such as acute hepatitis and active cirrhosis.
2) With liver disorders previously associated with methyldopa therapy.
3) With hypersensitivity to any component of this product.
4) On therapy with monoamine oxidase (MAO) inhibitors.

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. However, significant adverse effects due to methyldopa have been infrequent and this agent usually is well tolerated.
Cardiovascular: Aggravation of angina pectoris, congestive heart failure, prolonged carotid sinus hypersensitivity, orthostatic hypotension (decrease daily dosage), oedema or weight gain, bradycardia.
Digestive: Pancreatitis, colitis, vomiting, diarrhoea, sialadenitis, sore or "black" tongue, nausea, constipation, distension, flatus, dryness of mouth.
Endocrine: Hyperprolactinemia.
Hematologic: Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia, hemolytic anemia; positive tests for antinuclear antibody, LE cells, and rheumatoid factor, positive Coombs test.
Hepatic: Liver disorders including hepatitis, jaundice, abnormal liver function tests Hypersensitivity: Myocarditis, pericarditis, vasculitis, lupus-like syndrome, drug-related fever, and eosinophilia.
Nervous System/Psychiatric: Parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements, symptoms of cerebrovascular insufficiency, psychic disturbances including nightmares and reversible mild psychoses or depression, headache, sedation, asthenia or weakness, dizziness, light-headedness, paresthesias.
Metabolic: Rise in BUN.
Musculoskeletal: Arthralgia, with or without joint swelling; myalgia.
Respiratory: Nasal stuffiness.
Skin: Toxic epidermal necrolysis, rash.
Urogenital: Amenorrhea, breast enlargement, gynecomastia, lactation, impotence, decreased libido.

OVERDOSAGE :
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, diarrhea, nausea, vomiting).

PRECAUTIONS AND WARNINGS :
With prolonged methyldopa therapy, 10 to 20 percent of patients develop a positive direct Coombs test which usually occurs between 6 and 12 months of methyldopa therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anaemia, which could lead to potentially fatal complications. Before treatment is started, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anaemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy.
Rarely, fatal hepatic necrosis has been reported after use of methyldopa. These hepatic changes may represent hypersensitivity reactions. Periodic determinations of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction. Some patients taking methyldopa experience clinical edema or weight gain which may be controlled by use of a diuretic. Methyldopa should not be continued if edema progresses or signs of heart failure appear. Hypertension has recurred occasionally after dialysis in patients given methyldopa because the drug is removed by this procedure.
Nursing Mothers
Methyldopa appears in breast milk. Therefore, caution should be exercised when methyldopa is given to a nursing woman.

STORAGE : Store under normal storage conditions (15°C to 30°C) Protect from light.

Keep all medicines out of reach of children.

PRESENTATION : Jar pack of 1000 Tablets.
Blister pack of 10 x 10 Tablets.
Blister pack of 100 x 10 Tablets.

Manufactured in India by:
AGOG PHARMA LTD.
Plot No. 33, Sector II, The Vasai Taluka Indl.
Co-op. Estate Ltd., Vasai (E), Dist. Thane. INDIA.