SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRODUCT NAME

GENERIC: Methyldopa Tablets BP 250 mg-M DOPAKANT 250

BRAND NAME: M DOPAKANT 250

DESCRIPTION:

White to yellowish white coloured, circular, film coated, biconvex tablets plain on both side.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Methyldopa BP equivalent to

Anhydrous Methyldopa 250mg

Excipients ..... q.s.

Colour : Titanium Dioxide

For complete list of excipients refer section 6.1.

3. PHARMACEUTICAL FORM:

Solid Oral Dosage Form- Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication:

Treatment of hypertension.

4.2 Posology and method of administration:

Since Methyldopa is largely excreted by the kidneys, patients with impaired renal function may respond to comparatively low doses.

Withdrawal of Methyldopa which is followed by return of hypertension, usually within 48 hours, is not complicated generally by an overshoot of blood pressure.

Therapy with Methyldopa 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, Methyldopa should be limited to an initial dose of not more than 500mg daily and increased as required at intervals of not less than two days.

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 2g of Methyldopa daily.

Methyldopa may also be used concomitantly with the combination of amiloride hydrochloride and hydrochlorothiazide 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.

4.3 Contraindications:

• Active hepatic disease (such as acute hepatitis and active cirrhosis);

• Hypersensitivity (including hepatic disorders associated with previous methyldopa therapy) to methyldopa or any of the ingredients in the tablets;

• Phaeochromocytoma;

• Depression;

• Therapy with monoamine oxidase inhibitors (MAOIs)

4.4 Warning and precautions for use

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, also may 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.

The development of a positive direct Coombs' test occurs in 10-20% of patients and is dose related, the lowest incidence occurring in patients receiving 1g or less of methyldopa daily. It rarely develops in the first six months of treatment and if not encountered within twelve months is unlikely to occur. The test becomes negative usually within weeks or months of cessation of 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.

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 made for haemolysis; if present therapy should be discontinued. Stopping therapy with or without giving corticosteroid has usually brought prompt remission, however, rarely deaths have occurred.

Reversible leucopenia with primary effect on granulocytes has been reported rarely, but the granulocyte count has reverted back to normal on discontinuing therapy. Reversible thrombocytopenia has occurred rarely.

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

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.

Methyldopa should be used with extreme caution in patients, or in near relatives of patients, with hepatic porphyria.

4.5 Drug Interactions

Alcohol: concomitant use may enhance the hypotensive effect.

Alprostadil: concomitant use may enhance the hypotensive effect.

Anaesthetics: as concomitant use may enhance the hypotensive effect, patients may require reduced doses of anaesthetics when on methyldopa. If hypotension does occur during anaesthesia, it can usually be controlled by vasopressors.

Analgesics: NSAIDs antagonise the hypotensive effect.

Antibacterials: concomitant use with linezolid should be avoided as the hypotensive effect may be enhanced.

Antidepressants: concomitant use may enhance the hypotensive effect. Concomitant use with MAOIs should be avoided.

Antihypertensives: the use of other antihypertensives may enhance the hypotensive effect. The progress of patients should be carefully monitored to detect side-effects or manifestations of drug idiosyncrasy.

Antipsychotics: concomitant use can increase the risk of extrapyrimidal effects and enhance the hypotensive effect.

Anxiolytics and hypnotics: concomitant use may enhance the hypotensive effect.

Beta-blockers: concomitant use may enhance the hypotensive effect.

Calcium-channel blockers: concomitant use may enhance the hypotensive effect.

Corticosteroids: concomitant use may antagonise the hypotensive effect.

Diuretics: concomitant use may enhance the hypotensive effect.

Dopaminergics: concomitant use may antagonise the antiparkinsonian effect of this type of medicine. Concomitant use with levodopa or entacapone may enhance the hypotensive effect.

Iron: concomitant use may reduce the hypotensive effect. 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.

Lithium: when methyldopa and lithium are given concomitantly the patient should be monitored carefully for symptoms of lithium toxicity. Neurotoxicity may occur without increased plasma-lithium concentration.

Moxisylyte: concomitant use may enhance the hypotensive effect.

Muscle relaxants: concomitant use with baclofen and tizanidine may enhance the hypotensive effect.

Nitrates: concomitant use may enhance the hypotensive effect.

Oestrogens and progestogens: oestrogens and combined oral contraceptives antagonise the hypotensive effect.

Beta2 sympathomimetics: acute hypotension has been reported with salbutamol infusion.

Ulcer-healing drugs: carbenoxolone antagonises the hypotensive effect.

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 the colorimetric method. Interference of the latter with spectrophotometric methods have 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 phaeochromocytoma.

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.

Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites

4.6 Pregnancy & Lactation

Pregnancy:

There is no, or inadequate, evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence, animal studies having shown no hazard. If drug therapy is needed in pregnancy, this drug can be used if there is no safer alternative.

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

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 Adverse Effects

The most common side-effect of methyldopa is drowsiness. This is usually transient and may occur during the initial period of therapy or when the dose is increased. Other side-effects are rare, but the following have been reported:

Allergic: Drug-related fever and lupus-like syndrome, myocarditis, pericarditis.

Blood and lymphatic system disorders: Positive Coombs test, haemolytic anaemia, bone marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia, rise in blood urea. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Endocrine disorders: Hyperprolactinaemia.

Nervous system disorders: Sedation (usually transient), headache, asthenia or weakness, paraesthesiae, 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).

Cardiac disorders: 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).

Respiratory, thoracic and mediastinal disorders: Nasal stuffiness.

Gastrointestinal disorders: Nausea, vomiting, distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hpato-biliary disorders: Liver disorders including hepatitis, jaundice, abnormal liver function tests.

Skin and subcutaneous tissue disorders: Rash as in eczema or lichenoid eruption, toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders: Mild arthralgia with or without joint swelling, myalgia.

Reproductive system and breast disorders: Amenorrhoea, breast enlargement, gynaecomastia, lactation, failure of ejaculation, impotence, decreased libido.

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 and vomiting).

If ingestion is recent emesis may be induced or gastric lavage performed. There is no specific antidote, but Methyldopa is dialysable.

Treatment is largely symptomatic but if necessary intravenous infusion may be given to promote urinary excretion and pressor agents given cautiously.

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 Methyldopa should be discontinued.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Mechanism of Action:

Methyldopa is an antihypertensive agent which may act centrally by stimulating α2-adrenergic receptors.

5.2 Pharmacokinetic properties

Absorption

Methyldopa is incompletely and variably absorbed from the GI tract. It is partly conjugated, mainly to the O-sulphate, and is excreted by the kidneys. Elimination follows a biphasic pattern with a half-life of about

1.7 hours during the initial phase. Plasma protein binding is reported to be minimal. It crosses the placenta and small amounts appear in breast milk.

Distribution

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

Elimination

Drug and its metabolites are excreted in urine; unabsorbed drug is excreted unchanged in feces. Elimination half-life is about 2 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyldopa BP, Citric Acid Monohydrate BP, Disodium Edetate BP, Ethyl Cellulose 22CPS BP , Guar (Guar gum) BP, Colloidal Silicon Dioxide BP, Magnesium Stearate BP, Isopropyl Alcohol BP, Titanium dioxide(Wincoat-WT-1003)IHS, Methylene chloride BP.

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months

6.4 Special precautions for storage:

Do not store above 30°C. Protect from light. Do not freeze.

Keep the medicine out of reach of children.

6.5 Nature and contents of container

10 tablets in a blister.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements

7. APPLICANT

Manufactured by:

1802-1805, G.I.D.C., Phase III,

Vapi - 396 195. Gujarat, INDIA.

8. WHO PREQUALIFICATION REFERENCE NUMBER

Not applicable

9. DATE OF PREQUALIFICATION / RENEWAL OF PREQUALIFICATION

Not applicable

10. DATE OF REVISION OF THE TEXT

Not applicable