BOND CHEMICAL IND. Ltd

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SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

BONDOMET TABLETS (METHYLDOPA 250mg)

1. NAME OF THE MEDICINAL PRODUCT

Bondomet Tablets

Methyldopa Tablets BP 250mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active:	Per Tablet:
Methyldopa Ph.Eur	281.960 mg equivalent to methyldopa anhydrous 250mg

Excipient(s) with known effect

Each tablet contains 26.907 mg of lactose (as monohydrate).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Each tablet is yellowish, 10.7 mm, round and convex, embossed on one side with “B’DOMET” and on the other side with bond logo.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment of moderate to severe hypertension.

4.2 Posology and method of administration

ADULTS:

250mg 2-3 times daily for 2 days, adjusted at intervals of 2 days until adequate response is obtained. Maximum dose 3g daily (increase evening dose first). Usual effective dose 500mg to 2g daily.

ELDERLY:

Initial dose should be kept as low as possible not exceeding 250mg daily. An appropriate starting dose would be 125mg twice daily, increased slowly as required but not exceeding a maximum daily dosage of 2g.

CHILDREN:

10mg/kg bodyweight daily in 2-4 divided doses. The dosage is increased or decreased until adequate response is achieved. Maximum recommended daily dose is 65mg/kg bodyweight or 3g whichever is less.

4.3 Contraindications

Methyldopa tablets are contraindicated in patients with:

•Hypersensitivity to methyldopa or to any of the excipients listed in section 6 (including hepatic disorders associated with previous methyldopa therapy)

•A history of depression

•Active hepatic disease such as acute hepatitis and active cirrhosis

•On therapy with monoamine oxidase inhibitors (MAOIs)

•Porphyria

•Methyldopa Tablets are not recommended for the treatment of phaeochromocytoma or paraganglioma (see 4.4 'Special warnings and precautions for use').

4.4 Special warnings and precautions for use

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 done for haemolysis. If haemolytic anaemia is present, Methyldopa tablets should be discontinued. Stopping therapy, with or without giving a corticosteroid, has usually brought prompt remission. Rarely, however, deaths have occurred.

Some patients on continued therapy with methyldopa develop a positive Coombs test. From the reports of different investigators, the incidence averages between 10% and 20%. A positive Coombs test rarely develops in the first six months of therapy, and if it has not developed within 12 months, it is unlikely to do so later on continuing therapy. Development is also dose- related, the lowest incidence occurring in patients receiving 1 g or less of methyldopa per day. The test becomes negative usually within weeks or months of stopping 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.

Reversible leucopenia, with primary effect on granulocytes has been reported rarely. The granulocyte count returned to normal on discontinuing therapy. Reversible thrombocytopenia has occurred rarely.

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.

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.

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

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 colorimetric method. Interference with spectrophotometric methods for AST (SGOT) analysis has 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 or paraganglioma.

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

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 with other antihypertensive drugs, potentiation of antihypertensive action may occur. The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy. Concurrent use of verapamil and methyldopa can intensify sinus bradycardia.

Other classes of drugs:

The antihypertensive effect of methyldopa may be diminished by sympathomimetics, tricyclic antidepressants, phenothiazine derivatives and monoamine oxidase inhibitors (MAOIs), when administered concomitantly with these drugs (see 4.3 'Contra-indications'). In addition, phenothiazines may have additive hypotensive effects.

Concomitant administration of methyldopa with thiazide diuretics and other antihypertensive agents, general anaesthetics and levodopa enhances the antihypertensive effect.

The toxicity of haloperidol may be increased by concurrent use. Monoamine oxidase inhibitors should be discontinued before treatment with methyldopa.

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

Methyldopa has been used under close medical supervision for the treatment of hypertension during pregnancy. There is no clinical evidence of foetal abnormalities or effect on the neonate.

Published reports of the use of methyldopa during all trimesters indicate that if this drug is used during pregnancy the possibility of foetal harm appears remote.

Breast-feeding

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

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 or who are breast-feeding their newborn infant requires that anticipated benefits be weighed against possible risks.

4.7 Effects on ability to drive and use machines

Caution should be observed when driving or operating machinery, as methyldopa therapy may result in drowsiness, dizziness, light headedness, involuntary choreoathetotic movements in patients with severe cerebrovascular disease. The patient should be advised accordingly on initiation of therapy and/or increase in dosage.

4.8 Undesirable effects

The following convention has been utilised for the classification of frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	**Adverse event term**	**Frequency**
Cardiac disorders	Bradycardia, aggravation of angina pectoris, myocarditis, pericarditis, atrioventricular block	Not known
Blood and lymphatic system disorders	Haemolytic anaemia, bone-marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia	Not known
Nervous system disorders	Sedation (usually transient)*, headache**, paraesthesia, Parkinsonism, VIIth nerve paralysis, choreoathetosis*, mental impairment, carotid sinus syndrome, dizziness*, light-headedness*, symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)	Not known
Respiratory, thoracic and mediastinal disorders	Nasal Stuffiness	Not known
Gastrointestinal disorders	Nausea, vomiting, abdominal distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or 'black' tongue, pancreatitis	Not known
Skin and subcutaneous tissue disorders	Rash as in eczema or lichenoid eruption, toxic epidermal necrolysis, angioedema, urticaria	Not known
Musculoskeletal and connective tissue disorders	Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia	Not known
Endocrine disorders	Hyperprolactinaemia	Not known
Infections and Infestations	Sialadentis	Not known
Vascular disorders	Orthostatic hypotension (decrease daily dosage)	Not known
General disorders and administrative site conditions	Asthenia or weakness**, oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear.), drug-related fever	Not known
Hepatobiliary disorders	Liver disorders including hepatitis, jaundice	Not known
Reproductive system and breast disorders	Breast enlargement, gynaecomastia, amenorrhoea, lactation, impotence, failure of ejaculation	Not known
Psychiatric disorders	Psychic disturbances including nightmares, reversible mild	Not known

	psychoses or depression, decreased libido	
Investigations	Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, rise in blood urea	Not known

*Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. If affected, patients should not attempt to drive, or operate machinery.

**Headache, asthenia or weakness may be noted as early and transient symptoms.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorization 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 via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose may include acute hypotension, sedation, weakness, bradycardia, dizziness, gastrointestinal disturbances, light-headedness, constipation, distension, flatus, diarrhoea, nausea and vomiting.

Stomach emptied by aspiration, lavage and emesis may be induced if ingestion is recent. There is no specific antidote. Methyldopa is dialyzable. Treatment is symptomatic. Intravenous infusion may be given to promote urinary excretion and pressor agents such as metaraminol or noradrenaline given. Special care is needed with cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity. When chronic overdosage is suspected, methyldopa should be discontinued.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Methyldopa is an antihypertensive agent acting centrally by stimulating alpha adrenergic receptors. It inhibits the decarboxylation of dopa to dopamine but this action is not responsible for the hypotensive effect. It is suggested that a metabolite, alpha methylnoradrenaline may act as a false transmitter in the CNS. It reduces tissue concentration of dopamine noradrenaline, adrenaline and serotonin.

5.2 Pharmacokinetic properties

Methyldopa is incompletely absorbed from the gastrointestinal tract. Methyldopa is extensively metabolised through pathways common to the catecholamines utilising dopa decarboxylates and dopamine B-hydroxylase.

Decarboxylation is stereospecific. The bioavailability of an oral dose averages 25%(± 16%) and peak plasma levels occur 2 to 3 hours later. Elimination is biphasic. It is partly conjugated mainly to the o-sulphate and is excreted by the kidneys.

The elimination half-life is 1.8 ± 0.2 hours, methyldopa has been shown to cross the placental barrier and is found in the lungs, heart and muscles after 24 hours, detectable quantities are present in the liver and kidneys.

5.3 Preclinical safety data

None.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Citric Acid

EDTA

Lactose

Povidone

Ethanol

Purified Talc

Magnesium Stearate

Maize Starch

Film coating

Isopropyl Alcohol

Methylene Chloride

Tab coat Yellow TC 5132

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special Precautions for Storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and Contents of Container

Primary packaging:

The primary packs are blister pack (composed of printed Aluminium foil and 176mm Transparent PVC foil.

6.6 Special precautions for disposal <and other handling>

No special requirements.

Secondary packaging: Final pack is a grey, white and blue inner carton containing ten blister packs of ten tablets each

Special precautions for disposal

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

7. APPLICANT/MANUFACTURER

Bond chemical Industries Limited

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Awe, Oyo State, Nigeria.