SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

MEDOMET 500 mg Tablets
Methyldopa 500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Methyldopa BP 565 mg (equivalent to 500 mg anhydrous methyldopa).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Yellow film-coated biconvex tablets, engraved Medomet 500 on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of hypertension

4.2 Posology and method of administration

Posology

Adults:

Initial dosage: Usually 250 mg tablet Methyldopa twice or thrice a day for two days.

Adjustment: Usually adjusted at an interval of not less than two days until an adequate response is obtained. It is recommended that a thiazide diuretic be introduced to the regime if effective control cannot be maintained on 8 x 250 mg Methyldopa daily. The use of thiazide diuretics complements the effectiveness of Methyldopa and may be used either initially or at any stage during therapy. The maximum recommended daily dose is 3 grammes of Methyldopa.

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.

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

Patients with renal impairment:

Patients with impaired renal function may respond to smaller doses of the drug as Methyldopa is largely excreted by the kidneys.

Tolerance if it occurs is most likely to be seen in the second and third months after the commencement of therapy, and this may be overcome by increasing the dosage of Methyldopa or adding a thiazide diuretic.

Substitution of Methyldopa for other Antihypertensive Therapies:

i	Rauwolfia derivatives (reserpine), Mebutamate and Hydralazine whether used in combination or alone should be discontinued immediately. A starting dosage of one Methyldopa 250 mg tablet twice a day and increasing as necessary by one Methyldopa 250 mg tablet at weekly intervals.
ii	Adrenergic and ganglion blocking agents either used alone or in combination with those agents listed above should be progressively and cautiously withdrawn. In the first week of transfer for example the dosage of the blocking may be reduced by half and Methyldopa added at dosage level of one Methyldopa 250 mg tablet twice a day. In the second and third weeks the dosage of the blocking agent may be reduced to one quarter of its original while that of Methyldopa should be increased (or decreased) by 1 or 2 Methyldopa 250 mg tablet at three to seven day intervals in order that optimum control of blood pressure may be maintained. The blocking agent may thereafter be discontinued and the dosage of Methyldopa further adjusted as found necessary in order to control blood pressure at an optimum level.
iii	Discontinue hypotensive agents of the monoamine oxidase inhibitor group immediately and commence therapy with Methyldopa cautiously with one Methyldopa tablet twice a day. Although the immediate use of Methyldopa is not contra-indicated it may be advisable to delay the introduction of Methyldopa tablets until blood pressure starts to rise.
iv	Thiazide diuretics may be continued. When 500 mg of Methyldopa is added to 50 mg of hydrochlorothiazide, the two agents may be given together once daily.

Paediatric population:

Initial dosage is based on 10 mg/kg of bodyweight daily in 2-4 oral 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.

Elderly:

The initial dose for elderly patients should be kept as low as possible and not exceed 250 mg daily; an appropriate starting dose in the elderly would be 125 mg b.d. increasing slowly as required, but not to exceed a maximum daily dosage of 2 g.

Syncope in older patients may be related to an increased sensitivity and advanced arterioclerotic vascular disease. This may be avoided by lower doses.

Method of administration: Oral

4.3 Contraindications

Methyldopa is contra-indicated in patients with:

- Hypersensitivity to the active substance (including hepatic disorders associated with previous methyldopa therapy), or to any of the excipients listed in section 6.1.
- Active liver disease, such as acute hepatitis and active cirrhosis

- Depression
- On therapy with monoamine oxidase inhibitors (MAOIs)
- A catecholamine-secreting tumour such as phaeochromocytoma or paraganglioma
- Porphyria

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 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% of patients. 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 count are advisable 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.

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 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 the breakdown of methyldopa or its metabolites.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium:
Patients should be monitored for symptoms of lithium toxicity if methyldopa and lithium are given concurrently.

Other antihypertensive drugs:
Potentiation of the antihypertensive action of methyldopa may occur when this drug is used with other hypertensive agents. The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy.

Other classes of drug:
The antihypertensive effect of methyldopa may be diminished by sympathomimetics, phenothiazines, tricyclic antidepressants and MAOIs (see 4.3 'Contra-indications'). In addition, phenothiazines may have additive hypotensive effects.

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 was no clinical evidence that Methyldopa caused foetal abnormalities or affected 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. Methyldopa crosses the placental barrier and appears in the cord blood. Although no obvious teratogenic effects have been reported, foetal damage cannot be excluded and the use of drug in women who are, or who may become, pregnant requires that anticipated benefits be weighed against the possible risks.

Breast-feeding

Methyldopa appears in breast milk. The use of the drug in breast-feeding mothers requires that anticipated benefits be weighed against possible risks.

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 or operating machinery.

4.8 Undesirable effects

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.

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
Infections and infestations	Sialoadenitis	Not known
Blood and lymphatic system disorders	Haemolytic anaemia, bone-marrow failure, leukopenia, granulocytopenia, thrombocytopenia, eosinophilia	Not known
Endocrine disorders	Hyperprolactinaemia	Not known
Psychiatric disorders	Psychiatric disturbances including nightmares, reversible mild psychoses or depression, decreased libido	Not known
Nervous system disorders	Sedation (usually transient), headache, paraesthesia, parkinsonism, VIIth nerve paralysis, choreoathetosis, mental impairment, carotid sinus syndrome, dizziness, symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)	Not known
Cardiac disorders	Bradycardia, angina pectoris, myocarditis, pericarditis, atrioventricular block	Not known
Vascular disorders	Orthostatic hypotension (decrease daily dosage)	Not known
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Not known
Gastrointestinal disorders	Nausea, vomiting, abdominal distension, constipation, flatulence, diarrhoea, colitis, dry mouth, glossodynia, tongue discolouration, pancreatitis	Not known

Hepatobiliary disorders	Liver disorders including hepatitis, jaundice	Not known
Skin and subcutaneous tissue disorders	Rash (eczema, 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
Reproductive system and breast disorders	Breast enlargement, gynaecomastia, amenorrhoea, lactation disorder, erectile dysfunction, ejaculation failure	Not known
General disorder and administrative site conditions	Asthenia, oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear). Pyrexia.	Not known
Investigations	Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, increased blood urea	Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Acute overdosage may produce acute hypotension with other responses attributable to brain and gastro-intestinal malfunction (excessive sedation, weakness, dizziness, light headedness, bradycardia, distension, constipation, flatus, diarrhoea, nausea and vomiting).

Management

If ingestion is recent, emesis may be induced or gastric lavage should be performed. There is no specific antidote. Methyldopa is dialysable. Treatment is symptomatic. Infusions may be helpful to promote urinary excretion. Careful attention should be paid to cardiac rate and output, electrolyte balance, blood volume, urinary function, cerebral activity and paralytic ileus.

Administration of sympathomimetic agents may be indicated. When chronic overdosage is suspected, methyldopa should be discontinued.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiadrenergic agents; ATC code C02AB

Mechanism of action

It appears that several mechanisms of action account for the clinically useful effects of methyldopa and the current generally accepted view is that its principal action is on the central nervous system. The antihypertensive effect of methyldopa is probably due to its metabolism to alpha-methylnoradrenaline, which lowers arterial pressure by stimulation of central inhibitory alpha-adrenergic receptors, false neurotransmission, and/or reduction of plasma rennin activity. Methyldopa has been shown to cause a net reduction in the tissue concentrations of dopamine, norepinephrine (noradrenaline), epinephrine (adrenaline), and serotonin.

5.2 Pharmacokinetic properties

Absorption

Absorption of oral methyldopa is variable and incomplete.

Distribution

Bioavailability after oral administration averages 25%.

Biotransformation

Peak concentrations in plasma occur at two to three hours, and elimination of the drug is biphasic regardless of the route of administration. Plasma half-life is 1.8 ± 0.2 hours.

Elimination

Renal excretion accounts for about two thirds of drug clearance from plasma.

5.3 Preclinical safety data

No relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Citric Acid
Edetate calcium disodium
Ethylcellulose
Guar Gum
Microcrystalline Cellulose
Colloidal Anhydrous Silica
Magnesium Stearate

Coating:
Hydroxypropylmethylcellulose
Ethylcellulose
Opaspray K-1-6039
Diethyl Phthalate
Dispersed Yellow 14650 (E104)

6.2 Incompatibilities

None Stated.

6.3 Shelf life

Containers: 4 years
Blister packs: 2 years

6.4 Special precautions for storage

Store in a dry place below 25°C. Keep container well closed.

6.1 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polythene lids and polyurethane or polythene inserts.

Pack sizes: 56, 100 and 500

PVC/Aluminium blister pack

Pack size: 28 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Chelonia Healthcare Limited

Boumpoulinas 11, 3rd Floor

NICOSIA

CYPRUS

P.C. 1060

CYPRUS

8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/01/1988 10/12/1996

10 DATE OF REVISION OF THE TEXT

21/04/2021