

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TIMUCEN 250 (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg anhydrous methyldopa.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

TIMUCEN 250 are yellow, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Methyldopa (as in **TIMUCEN 250**) is indicated in the treatment of essential hypertension.

4.2. Posology and method of administration

Posology

Doses of 250 mg two or three times daily during the first 48 hours. Thereafter, the daily dosage may be adjusted preferably at intervals of not less than 48 hours, until an adequate response has been achieved. The usual dose is from 500 mg – 2 g daily.

Paediatric population

A suggested initial dose for children is 10 mg/kg body mass daily in divided doses.

Method of administration

For oral administration.

4.3. Contraindications

TIMUCEN 250 is contraindicated in:

- Persons known to be hypersensitive to methyldopa or its excipients, listed in section 6.1.
- Patients with impaired kidney or liver function or with a history of liver disease.
- Mental depression.
- It should not be given to patients with acute liver disease.
- Pheochromocytoma.
- Porphyria. Methyldopa (as in **TIMUCEN 250**) has been reported to aggravate porphyria.
- Patients on therapy with monoamine oxidase inhibitors (MAOI).

4.4. Special warnings and precautions for use

It is advisable to do periodic blood counts and to perform liver function tests at intervals during the first 6 to 12 weeks of treatment, or if the patient develops an unexplained fever.

Patients taking **TIMUCEN 250** may produce a positive response to a direct antiglobulin test (Coombs' test); if blood transfusion is required, prior knowledge of a positive direct antiglobulin test (Coombs' test) reaction will aid cross-matching.

Methyldopa may occasionally cause urine to darken because of the breakdown of the medicine or its metabolites.

Severe hypotension may occur during anaesthesia in patients being treated with methyldopa (as in **TIMUCEN 250**). Lower doses of general anaesthetics may be required.

The hypotensive effects may be diminished by sympathomimetics, imipramine and other tricyclic antidepressants and monoamine oxidase inhibitors.

4.5. Interaction with other medicines and other forms of interaction

- The hypotensive effects of methyldopa are enhanced by thiazide diuretics and other hypotensive agents.
- Methyldopa (as in **TIMUCEN 250**) may interfere with the measurement of urinary uric acid by the phosphotungstate method, and serum glutamic-pyruvic transaminase, by the colormetric method. Methyldopa fluoresces at the same wavelengths as catecholamines and may cause erratic reports of elevated urinary catecholamine concentration.
- Severe hypotension may occur during anaesthesia in patients being treated with **TIMUCEN 250**.
- The hypotensive effects may be diminished by sympathomimetics, phenothiazines, imipramine and other tricyclic antidepressants and monoamine oxidase inhibitors (see section 4.3).
- When **TIMUCEN 250** and lithium are given concomitantly the patient should be monitored carefully for symptoms of lithium toxicity.
- The combination of **TIMUCEN 250** with other potentially hepatotoxic medicines, particularly halothane, is not advisable.

4.6. Fertility, pregnancy and lactation

Pregnancy

The safety of **TIMUCEN 250** in pregnancy has not been established, as there are no adequate and well-controlled studies in pregnant women.

Methyldopa crosses the placenta and reduced blood pressure has been reported in infants born to mothers receiving **TIMUCEN 250**.

Lactation

Methyldopa is distributed into breast milk in small amounts. The safety of **TIMUCEN 250** in lactation has not been established.

4.7. Effects on ability to drive and use machines

The most common side-effect of methyldopa is drowsiness in the first 2 or 3 days; this usually decreases spontaneously (see section 4.8). Caution is advised when driving or using machinery.

4.8. Undesirable effects

a. Summary of the safety profile

The most common side-effect of methyldopa is drowsiness in the first 2 or 3 days; this usually decreases spontaneously or as a result of a reduction in the dosage.

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Less frequent	Salivary gland inflammation.
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia, leucopenia, granulocytopenia, and haemolytic anaemia. Fever may occur within the first few weeks of therapy and may be accompanied by eosinophilia and abnormal liver function tests.
Endocrine disorders	Less frequent	Hyperprolactinaemia.
Psychiatric disorders	Frequent	Depression, psychic effects, impaired mental acuity, nightmares.

Nervous system disorders	Frequent	Drowsiness, weakness, dizziness, light-headedness, headache.
	Less frequent	Paraesthesia, Bell's palsy, parkinsonism. Involuntary choreoathetotic movements have occurred in patients with severe bilateral cerebrovascular disease.
Cardiac disorders	Less frequent	Myocarditis, and aggravation of angina pectoris may occur. There may be bradycardia.
Vascular disorders	Less frequent	Postural hypotension.
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal stuffiness.
Gastrointestinal disorders	Frequent	Nausea, dryness of the mouth.
	Less frequent	Black or sore tongue, pancreatitis, gastrointestinal upsets, diarrhoea, constipation.
Hepatobiliary disorders	Frequency unknown	Jaundice with or without fever may occur. Liver damage may also develop after long-term administration and, rarely, fatal hepatic necrosis has been reported.
Skin and subcutaneous tissue disorders	Less frequent	Eczematous rashes and lichenoid and granulomatous skin eruptions have occurred.
Musculoskeletal and connective tissue disorders	Less frequent	Mild arthralgia, myalgia.
	Frequency unknown	A condition resembling systemic lupus erythematosus has been reported.
Reproductive system and breast disorders	Frequent	Disorders of sexual function.
	Less frequent	Breast enlargement, lactation.

General disorders and administration site conditions	Frequent	Oedema.
Investigations	Less frequent	Uraemia.
	Frequency unknown	A positive response to the direct Coombs' test may occur in 10 to 20 % of patients on prolonged therapy, usually without evidence of haemolysis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>

4.9. Overdose

See section 4.8 “Undesirable effects”. Treatment is symptomatic and supportive. Methyldopa is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 7.1.3- Other hypotensives.

Pharmacotherapeutic group: Antiadrenergic agents; ATC code: C02AB

Mechanism of action:

The exact mechanism of pharmacological action is not known but methyldopa may involve stimulation of central alpha-adrenergic receptors by a metabolite, alpha-

methylnorepinephrine, thus inhibiting sympathetic outflow to the heart, kidneys and peripheral vasculature.

Reduced peripheral resistance and plasma renin activity may also contribute to its effect.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core tablet:

Microcrystalline cellulose (Avicel pH 101)

Crospovidone CL-M (Type B)

Povidone

Magnesium Stearate

Tablet coating:

Citric Acid Monohydrate

Disodium Edetate

Opadry Yellow OY-8466, which includes Methocel ES Premium EP (E464); Titanium

Dioxide BP C.I. No. 77891 (E 171); Polyethylene Glycol 400; Quinoline Yellow Aluminium

Lake C.I. No. 47005 (E 104); and Iron Oxide Yellow C.I. No. 77492 (E 172).

6.2. Incompatibilities

None known.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store below 25 °C.

Keep the container tightly closed.

Protect from light and dispense in amber bottles.

6.5. Nature and contents of container

Aluminium/PVC/PYDC blister packs or polypropylene securitainer of 56, 84, 100 and 500 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

3 Gwen Lane, 4th Floor,

Sandton,

2031

Email: pv@trinitypharma.co.za

Contact number: +27 (0)10 594 5610

8. REGISTRATION NUMBER(S)

Y/7.1.3/134

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 January 1991

10. DATE OF REVISION OF THE TEXT

30 October 2024