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.
- Phaeochromocytoma.
- 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, gastro-intestinal 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-methylnorephinephrine, 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; Ouinoline 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 ºC.
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.
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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