PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE
THIMATRIN tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each uncoated tablet contains 5 mg of carbimazole.
Contains sugar: lactose anhydrous 70 mg per tablet.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Uncoated tablet.
White coloured, round shaped, uncoated tablets, debossed "5" on one side and break line on other side.

4 CLINICAL PARTICULARS
Therapeutic indications
THIMATRIN is indicated in the management of hyperthyroidism, thyrotoxicosis (including thyroid storm), and also for the preparation of patients for thyroidectomy.
THIMATRIN can also be used for therapy prior to and post radio-active ablative therapy.

Posology and method of administration
Posology
THIMATRIN should only be administered if hyperthyroidism has been confirmed by laboratory tests.
10 mg to 60 mg daily according to the severity of the disorder. The dose should be gradually reduced to the smallest amount which will control the disease.
Daily dosage should be divided and titrated against thyroid function until the patient is euthyroid in order to reduce the risk of over-treatment and resultant hypothyroidism.
Serial thyroid function monitoring is recommended, together with appropriate dosage modification in order to maintain a euthyroid state.

Method of administration
For oral use.

Contraindications
- Hypersensitivity to carbimazole, other thiourea antithyroid medicines, or to any of the excipients (see section 6.1).
- Serious, pre-existing haematological conditions.
- Severe hepatic insufficiency.
- Patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazole.
- Tracheal obstruction.

Special warnings and precautions for use
Bone marrow depression including neutropenia, eosinophilia, leucopenia and agranulocytosis has been reported. Fatalities with carbimazole-induced agranulocytosis have been reported.

Cases of pancytopenia/aplastic anaemia and isolated thrombocytopenia have also been reported. Additionally, cases of haemolytic anaemia have been reported.

Patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever and malaise and should be instructed to stop THIMATRIN and to seek medical advice immediately. In such patients, white blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection.

There have been post-marketing reports of acute pancreatitis in patients receiving carbimazole or its active metabolite thiamazole. In case of acute pancreatitis, THIMATRIN should be discontinued immediately. THIMATRIN must not be given to patients with a history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazole. Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset.

Following the onset of any signs and symptoms of hepatic disorder (pain in the upper abdomen, anorexia, general pruritus) in patients, THIMATRIN should be stopped and liver function tests performed immediately.

Early withdrawal of THIMATRIN will increase the chance of complete recovery.

THIMATRIN should be used with caution in patients with mild-moderate hepatic insufficiency. If abnormal liver function is discovered, the treatment should be stopped. The half-life may be prolonged due to the liver disorder.

THIMATRIN should be stopped temporarily at the time of administration of radio-iodine (to avoid thyroid crisis).

Patients unable to comply with the instructions for use or who cannot be monitored regularly should not be treated with THIMATRIN.

Regular full blood count checks should be carried out in patients who may be confused or have a poor memory.

Precaution should be taken in patients with intrathoracic goitre, which may worsen during initial treatment with THIMATRIN. Tracheal obstruction may occur due to intrathoracic goitre.

There is a risk of cross-allergy between carbimazole, the active metabolite thiamazole (methimazole) and propylthiouracil.

Women of childbearing potential and pregnancy
Women of childbearing potential have to use effective contraceptive measures during treatment. If THIMATRIN is used during pregnancy, the lowest effective dose without additional administration of thyroid hormones should be administered. Close maternal, foetal and neonatal monitoring is warranted (see section 4.6).

Lactose
THIMATRIN contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.
Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take THIMATRIN.

Interaction with other medicines and other forms of interaction
Particular care is required in case of concurrent administration of medicine capable of inducing agranulocytosis.
Since THIMATRIN is a vitamin K antagonist, the effect of anticoagulants could be intensified. Additional monitoring of prothrombin time/international normalised ratio (PT/INR) should be considered, especially before surgical procedures.

The serum levels of theophylline can increase and toxicity may develop if hyperthyroidic patients are treated with antithyroid medicines without reducing the theophylline dosage.

Co-administration of prednisolone and THIMATRIN may result in increased clearance of prednisolone.

THIMATRIN may inhibit the metabolism of erythromycin, leading to reduced clearance of erythromycin.

Serum digoxin levels may be increased when hyperthyroid patients on a stable digoxin regimen become euthyroid; a reduced dosage of digoxin may be needed.

Hyperthyroidism may cause an increased clearance of beta-adrenergic blockers with a high extraction ratio. A dose reduction of beta blockers may be needed when a hyperthyroid patient becomes euthyroid.

Laboratory value alterations
With diagnostic test results:
THIMATRIN may decrease thyroidal uptake of sodium iodide I 123 or I 131, or pertechnetate, withdrawal of THIMATRIN 5 days or more before radioactive iodine uptake tests is necessary to prevent interference.
With physiology laboratory test values:
Alanine aminotransferase (ALT [SGPT]) serum concentrations, alkaline phosphatase serum concentrations, aspartate aminotransferase (AST [SGOT]) serum concentrations, bilirubin serum concentrations, lactate dehydrogenase (LDH) serum concentrations and prothrombin time (PT) may be increased, and may indicate hepatoxicity and be associated with splenomegaly.
Fertility, pregnancy and lactation
Women of childbearing potential
Women of childbearing potential have to use effective contraceptive measures during treatment (see section 4.4).

Pregnancy
Safety in pregnancy and lactation has not been established. THIMATRIN may cause foetal or neonatal hypothyroidism and goitre. THIMATRIN crosses the placenta but, provided the mother's dose is within the standard range, and her thyroid status is monitored; there is no evidence of neonatal thyroid abnormalities. Cases of congenital malformations have been observed following the use of THIMATRIN or its active metabolite methimazole during pregnancy. A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenital, to transplacental exposure to THIMATRIN and methimazole cannot be excluded. Therefore, the use of THIMATRIN in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment. Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported.

Lactation
THIMATRIN is excreted in milk and if treatment is continued during lactation the patient should not continue to breastfeed her baby.

Effects on ability to drive and use machines
The effect on the ability to drive and use machines is not known.

Undesirable effects
a. Summary of the safety profile
Adverse reactions usually occur in the first eight weeks of treatment.
The most frequent minor reactions are nausea, headache, arthralgia, mild gastrointestinal disturbance, skin rashes and pruritus. These reactions are usually self-limiting and may not require withdrawal of the medicine.

b. Tabulated summary of adverse reactions
The undesirable effects are listed below by system organ class. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Bone-marrow depression including neutropenia, eosinophilia, leukopenia. Fatalities with carbimazole-induced, agranulocytosis have been reported (see section 4.4).
	Frequency unknown	Pancytopenia/aplastic anaemia, thrombocytopaenia, haemolytic anaemia
Immune system disorders	Less frequent	Angioedema, multi-system hypersensitivity reactions such as cutaneous vasculitis, liver, lung and renal effects
Endocrine disorders	Frequency unknown	Insulin autoimmune syndrome (with pronounced decline in blood glucose level)
Nervous system disorders	Frequent	Headache
	Frequency unknown	Paraesthesias, neuritis, polyneuropathy
Vascular disorders	Frequency unknown	Vassculitis, bleeding
Gastrointestinal disorders	Frequent	Gastrointestinal disturbances (including nausea, vomiting and gastric discomfort)
	Frequency unknown	Taste disturbances, acute salivary gland swelling, acute pancreatitis
Hepato-biliary disorders	Less frequent	Jaundice, abnormal liver function tests, hepatitis, cholestatic jaundice; in these cases of hepatic disorder THIMATRIN should be withdrawn and not re-introduced.
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, skin pigmentation, urticaria
	Less frequent	Severe cutaneous hypersensitivity reactions, including Stevens-Johnson syndrome (very rare including isolated reports: severe forms, including generalised dermatitis, have only been described in isolated cases).
	Frequency unknown	Abnormal hair loss
Musculoskeletal and connective tissue disorders	Less frequent	Myopathy, arthralgia. Patient experiencing myalgia after the intake of THIMATRIN should have their creatine phosphokinase levels monitored.
	Frequency unknown	Lupus-like syndrome
Renal and urinary disorders	Frequency unknown	Nephritis
General disorders and administration site conditions	Frequency unknown	Fever, malaise
Injury, poisoning and procedural complications	Frequency unknown	Bruising

Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults.

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

Overdose
Signs and symptoms
Overdosage or accidental poisoning may result in hypothyroidism and goitre. If blood dyscrasias occur, the medicine should be withdrawn immediately
Management of overdose
Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Sulfur-containing imidazole derivatives.
ATC Code: H03BB01
A.21.3 Thyroid preparations
Carbimazole is an anti-thyroid medicine which depresses the formation of thyroid hormone. It reduces the uptake and concentration of inorganic iodine by the thyroid, but its main effect is to reduce the formation of di-iodotyrosine and thyroxine.

Pharmacokinetic properties
Absorption
Carbimazole is rapidly metabolised to thiamazole. After oral ingestion, peak plasma concentrations of thiamazole, the active moiety, occur at 1 to 2 hours.

Distribution
The total volume of distribution of thiamazole is 0,5 l/kg. Thiamazole is concentrated in the thyroid gland. This intrathyroidal concentration of thiamazole has the effect of prolonging its activity. However, thiamazole has a shorter half-life in hyperthyroid patients than in normal controls and so more frequent initial doses are required while the hyperthyroidism is active.

Biotransformation
Thiamazole is moderately bound to plasma proteins. Carbimazole has a half-life of 5,3 to 5,4 hours. It is possible that the plasma half-life may also be prolonged by renal or hepatic disease (see section 4.2). Thiamazole crosses the placenta and appears in breast milk. The plasma: milk ratio approaches unity.

Elimination
Over 90 % of orally administered carbimazole is excreted in the urine as thiamazole or its metabolites. The remainder appears in faeces. There is 10 % enterohepatic circulation.

6 PHARMACEUTICAL PARTICULARS
List of excipients
Croscarmellose sodium
Lactose anhydrous
Magnesium stearate

Incompatibilities
Not applicable.

Shelf life
36 months

Special precautions for storage
Store at or below 25 ºC. Protect from moisture.
Keep in the original container until required for use.

Nature and contents of container
PVC/PE/PVDC/Aluminium foil blisters in brown coloured cartons of 20, 28, 30, 50, 56, 100 and 112 pack sizes.
Not all pack sizes may be marketed.

Special precautions for disposal
No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Strides Pharma SA (Pty) Ltd
106 16th Road
Building 2
Midrand
South Africa
1686

8 REGISTRATION NUMBER
THIMATRIN 54/21.3/0150.149

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25 July 2023

10 DATE OF REVISION OF THE TEXT

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