

# AUSTRALIAN PRODUCT INFORMATION – THIRAZOL (CARBIMAZOLE) TABLETS

## 1 NAME OF THE MEDICINE

Carbimazole.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Thirazol tablet contains 5 mg carbimazole as the active ingredient.

Excipients with known effect: contains sugars as lactose.

For the full list of excipients, see Section 6.1 List of Excipients.

## 3 PHARMACEUTICAL FORM

Thirazol 5 mg tablets are white, round, uncoated tablets debossed with CARB on one side and “5” on the other side, containing 5mg carbimazole.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Therapy of hyperthyroidism. Definitive therapy: induction of a permanent remission, in either primary or secondary thyrotoxicosis. Preparation for thyroidectomy. Before and after radioactive iodine treatment.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

It is customary to begin therapy with a dosage that will fairly quickly control the thyrotoxicosis and render the patient euthyroid, and later to reduce this.

The tablets are for oral administration.

#### **Adults**

#### Usual initial dosages

Mild cases, 15 to 20 mg/day in divided doses; moderate cases, 30 mg/day in divided doses; severe cases, 40 to 45 mg (up to 60 mg) /day in divided doses and should be titrated against thyroid function until the patient is euthyroid in order to reduce the risk of over-treatment and resultant hypothyroidism.

If large stores of hormone are present, as in nodular goitre, response to carbimazole may be delayed for several weeks or months, whereas in severe thyrotoxicosis, when very little hormone is stored, improvement may be detected within three to four days.

#### Maintenance dosage

When symptoms are controlled, the dosage should be reduced to a maintenance level, which will usually be between 10 and 15 mg daily.

Experience has shown there is a wide variation of sensitivity to the medicine from time to time in a particular patient. Serial thyroid function monitoring is recommended, together with appropriate dosage modification in order to maintain a euthyroid state. For this reason, patients should be seen monthly for the first year; and thereafter at 3 or 6 monthly intervals. Once a remission has been secured, maintenance dosage should be continued for at least 12 months, and up to 2 years of treatment may be required.

If thyroidectomy is intended, it can be carried out once the euthyroid state is achieved with Thirazol, which is then discontinued.

### Changeover from thiouracils

When treatment with one of the thiouracils is replaced by carbimazole therapy, 50 mg of methylthiouracil or propylthiouracil can be taken as equivalent to 5 mg of carbimazole.

### Delayed response to carbimazole therapy

If no relief is obtained within three months, the possible causes are: patients have failed to take their Thirazol medication (this is the most common cause); previous iodine therapy which has resulted in an increased hormone store within the gland; inadequate dosage of Thirazol.

### Preparation of thyrotoxic patients for surgery

Thirazol is prescribed prior to thyroidectomy and should then be given in sufficient dosage and for long enough to render the patient euthyroid. It should be continued up to the time of operation but should be prescribed together with iodide during the last 2 weeks.

### **Elderly**

No special dosage regimen is required, but care should be taken to observe the contraindications and warnings as it has been reported that the risk of a fatal outcome to neutrophil dyscrasia may be greater in the elderly (aged 65 or over).

## **4.3 CONTRAINDICATIONS**

Thirazol is contraindicated in patients with:

- a previous history of adverse reactions to carbimazole or to any of the excipients in the composition
- retrosternal goitre
- serious pre-existing haematological conditions
- severe hepatic insufficiency
- a history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazole.

Thirazol should be given with caution if there is any degree of tracheal obstruction, as high dosage may increase thyroid enlargement and aggravate obstructive symptoms.

## **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Thirazol should only be administered if hyperthyroidism has been confirmed by laboratory tests. Dosage should be 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 (see Section 4.2 Dosage and method of administration).

### **Agranulocytosis**

As fatal cases of agranulocytosis with carbimazole have been reported and early treatment of agranulocytosis is essential, it is important that patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever, malaise or other symptoms which might suggest bone marrow depression and should be instructed to stop the medicine and to seek medical advice immediately. In such patients, blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection. Early withdrawal of the medicine will increase the chance of complete recovery.

### **Anaemia**

Rare cases of pancytopenia/aplastic anaemia, and very rare cases of haemolytic anaemia and thrombocytopenia have been reported (see Section 4.8 Adverse effects).

### **Radio-iodine**

Thirazol should be stopped temporarily at the time of administration of radio-iodine.

### **Memory and compliance**

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

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

### **Hereditary disorders**

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

### **Intrathoracic goitre**

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

### **Pancreatitis**

There have been post-marketing reports of acute pancreatitis in patients receiving carbimazole or its active metabolite thiamazole. In case of acute pancreatitis, carbimazole should be discontinued immediately. Carbimazole 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.

### **Vasculitis**

Cases of vasculitis resulting in severe complications have been reported in patients receiving carbimazole and methimazole therapy. These cases of vasculitis include: leukocytoclastic cutaneous vasculitis, acute kidney injury and glomerulonephritis, alveolar/pulmonary haemorrhage, CNS vasculitis, and neuropathy. Most cases were associated with anti-neutrophilic cytoplasmic antibodies (ANCA)-positive vasculitis. In some cases, vasculitis resolved/improved with drug discontinuation; however, more severe cases required treatment with additional measures including corticosteroids, immunosuppressant therapy, and plasmapheresis. If vasculitis is suspected, discontinue therapy and initiate appropriate intervention.

### **Women of childbearing potential and pregnancy**

Women of childbearing potential must use effective contraceptive measures during treatment.

The use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see Section 4.6 Fertility, pregnancy and lactation, Use in pregnancy).

The use of carbimazole in pregnant women must be based on the individual benefit/risk assessment. If carbimazole 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 Fertility, pregnancy and lactation, Use in pregnancy).

### **Use in hepatic impairment**

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

Carbimazole 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.

### **Use in the elderly**

No data available.

### **Paediatric use**

No data available.

### **Effects on laboratory tests**

No data available.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

### **Thiamazole and Propylthiouracil**

Little is known about interactions. There is a risk of cross-allergy between carbimazole, thiamazole and propylthiouracil.

### **Agranulocytosis**

Particular care is required in case of concurrent administration of medicines capable of inducing agranulocytosis.

Since carbimazole is a vitamin K antagonist, the effect of anticoagulants could be intensified. An accurate control with regards to the anticoagulant dosage is required as hyperthyroid patients receiving treatment with carbimazole become euthyroid; additional monitoring of prothrombin time/international normalised ratio (PT/INR) should be considered, especially before surgical procedures. Carbimazole administration may itself, rarely, result in hypoprothrombinaemia, which may increase the risk of haemorrhagic events.

### **Antithyroid medicines**

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

### **Prednisolone**

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

### **Erythromycin**

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

### **Digitalis glycosides**

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

### **Beta blockers**

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.

### **Paediatric patients**

Interaction studies have not been performed in paediatric patients.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

There is no information on impairment of fertility following treatment with carbimazole

### **Use in pregnancy – Pregnancy Category D**

*Carbimazole is Pregnancy Category D – Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

Antithyroid agents may cause congenital goitre by inhibiting thyroxine synthesis in the foetus. During pregnancy these products should therefore only be used after carefully weighing the mother's needs against the risk to the foetus.

Studies have shown that the incidence of congenital malformations is greater in the children of mothers whose hyperthyroidism has remained untreated than in those who have been treated with carbimazole. However, very rare cases of congenital malformations have been observed following the use of carbimazole or its active metabolite methimazole during pregnancy. Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformations and duodenal atresia have been reported. A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenital, to transplacental exposure to carbimazole and methimazole cannot be excluded. Therefore, carbimazole should be used in pregnancy only when propylthiouracil is not suitable (see Section 4.4 Special warnings and precautions for use).

The basal metabolic rate is raised during pregnancy and the dosage of Thirazol must be adjusted accordingly. The smallest dose compatible with rendering the patient symptom free should be employed. The dosage during the last 3 months of pregnancy should, if possible, not exceed 15 mg twice daily.

Thirazol should be discontinued 3 to 4 weeks before delivery and a course of iodine should be substituted. The danger of producing hypothyroid babies as a result of low dosage antithyroid therapy during pregnancy appears to have been grossly exaggerated.

Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.

Carbimazole is able to cross the human placenta.

Based on human experience from epidemiological studies and spontaneous reporting, carbimazole is suspected to cause congenital malformations when administered during pregnancy, particularly in the first trimester of pregnancy and at high doses.

Reported malformations include aplasia cutis congenita, craniofacial malformations (choanal atresia; facial dysmorphism), exomphalos, oesophageal atresia, omphalo- mesenteric duct anomaly, and ventricular septal defect.

Carbimazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. If carbimazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended (see Section 4.4 Special warnings and precautions for use).

#### Women of childbearing potential

Women of childbearing potential must use effective contraceptive measures during treatment (see Section 4.4 Special warnings and precautions for use).

#### **Use in lactation**

Carbimazole and related medicines cross the placenta and are concentrated in the breast milk. Infants should not be breastfed by mothers taking carbimazole.

### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

### **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

All toxic reactions to carbimazole occurred within 8 weeks of starting treatment, and there was no reaction in patients who received 20 mg or less of carbimazole per day. The most common minor side effects are nausea, headache, arthralgia and mild gastric distress. Mild skin rashes and pruritus can occur and these often respond to antihistamines without discontinuation of the medicine.

Adverse reactions are listed according to frequency, starting with the most frequent, and according to the following classification:

Very common	≥ 1/10
Common	≥ 1/100, < 1/10
Uncommon	≥ 1/1,000, < 1/100
Rare	≥ 1/10,000, < 1/1,000
Very rare	< 1/10,000
Not known	cannot be estimated from the available data

### **Blood and lymphatic system disorders**

Of the major toxic reactions to carbimazole, bone marrow depression including neutropaenia, eosinophilia, leukopaenia and agranulocytosis are the most serious. Fatalities with carbimazole-induced agranulocytosis have been reported.

Rare: pancytopenia/aplastic anaemia.

Very rare: haemolytic anaemia, thrombocytopenia.

Patients should be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever, and malaise (see Section 4.4 Special warnings and precautions for use).

### **Immune system disorders**

Angioedema and multi-system hypersensitivity can cause liver, lung and renal effects. There are reports of vasculitis, often associated with the presence of anti-neutrophilic cytoplasmic antibodies (ANCA), resulting in severe complications (see Section 4.4 Special warnings and precautions for use).

### **Endocrine disorders**

Not known: insulin autoimmune syndrome (with significant reduction in blood glucose levels).

### **Nervous system disorders**

Headache, neuritis.

### **Vascular disorders**

Bleeding.

### **Gastrointestinal system disorders**

Nausea, mild gastric distress, loss of sense of taste.

Not known: acute pancreatitis.

### **Hepatobiliary disorders**

Hepatic disorders including abnormal liver function tests, hepatitis, cholestatic hepatitis, cholestatic jaundice and most commonly jaundice, have been reported; in these cases carbimazole should be withdrawn.

### **Skin and subcutaneous tissue disorders**

Skin rash, pruritus, urticaria, hair loss.

Severe cutaneous hypersensitivity reactions have been reported in both adults and paediatric patients, including generalised dermatitis and Stevens-Johnson syndrome (very rare).

### **Musculoskeletal and connective tissue disorders**

Arthralgia.

Isolated cases of myopathy were reported in patients complaining from myalgia. Monitoring of creatine phosphokinase (CPK) levels is recommended in these instances.

## **General disorders and administration site conditions**

Fever, malaise.

## **Injury, poisoning and procedural complications**

Not known: bruising.

## **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **4.9 OVERDOSE**

### **Symptoms**

The principle manifestations of poisoning are skin rash and leukopaenia. Acute poisoning has not been reported.

### **Treatment**

Treat toxic neuropathy by physiotherapy.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

Carbimazole is an anti-thyroid agent.

Carbimazole is believed to exert its antithyroid effect by 'blocking' the organic binding of iodine through inhibition of the iodination of tyrosine. It is also thought to have some action on peroxidase which is required as a catalyst in the synthesis of thyroxine by the thyroid gland. It does not affect the uptake of iodine by the thyroid gland and this is of vital importance in the treatment of thyrotoxicosis with radioactive iodine or with a combination of radioiodine and carbimazole, and also in preparation of patients for operation.

#### **Clinical trials**

No data available.

### **5.2 PHARMACOKINETIC PROPERTIES**

#### **Absorption**

Carbimazole is rapidly absorbed from the gastrointestinal tract.

#### **Metabolism**

Carbimazole is completely and rapidly metabolised to methimazole and it is the latter that is responsible for the antithyroid activity of carbimazole. The mean peak plasma concentration of methimazole is reported to occur one hour after a single dose of carbimazole. The plasma half-life of methimazole is reported as between 3 and 6 hours.

#### **Excretion**

Most of an orally administered dose of carbimazole is excreted in the urine. Less than 12% may be excreted as unchanged methimazole.

### 5.3 PRECLINICAL SAFETY DATA

#### Genotoxicity

No data available.

#### Carcinogenicity

No data available.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Lactose, croscarmellose sodium, magnesium stearate.

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

### 6.5 NATURE AND CONTENTS OF CONTAINER

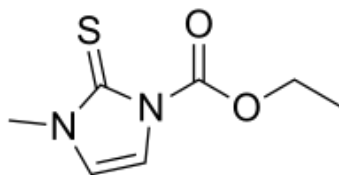
White, round HDPE bottle with child-resistant polypropylene closure and silica gel desiccant. Each bottle contains 100 tablets.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

#### Chemical structure



Chemical name: ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate.

Molecular formula: C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S

Molecular weight: 186.2 g/mol

Carbimazole is a white or yellowish-white crystalline powder, slightly soluble in water, soluble in alcohol and in acetone.

#### CAS number

22232-54-8

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine



## **8 SPONSOR**

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## **9 DATE OF FIRST APPROVAL**

17 August 2023

## **10 DATE OF REVISION**

Not applicable

### **10.1 SUMMARY TABLE OF CHANGES**

<b>Section Changed</b>	<b>Summary of new information</b>
all	new PI