# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Carbimazole 5 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of carbimazole

Excipient with known effect:

Each tablet contains 70 mg of lactose anhydrous.

For a full list of excipients see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

White coloured, 6.30 mm round shaped uncoated tablets, debossed”5” on one side and a break line on the other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Carbimazole is an anti-thyroid agent. It is indicated in adults and children in all conditions where reduction of thyroid function is required.

Such conditions are:

1.Hyperthyroidism.

2.Preparation for thyroidectomy in hyperthyroidism.

3 Therapy prior to and post radio-iodine treatment.

## 4.2 Posology and method of administration

Carbimazole should only be administered if hyperthyroidism has been confirmed by laboratory tests.

Posology

Older people

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).

Paediatric population

Use in children and adolescents (3 to 17 years of age)

The usual initial daily dose is 15 mg per day adjusted according to response.

Use in children (2 years of age and under)

Safety and efficacy of carbimazole in children below 2 years of age have not been evaluated systematically. Use of carbimazole in children below 2 years of age is therefore not recommended.

Adults

The initial dose is in the range 20 mg to 60 mg, taken as two to three divided doses. The dose should be titrated against thyroid function until the patient is euthyroid in order to reduce the risk of over-treatment and resultant hypothyroidism.

Subsequent therapy may then be administered in one of two ways.

Maintenance regimen: Final dosage is usually in the range 5 mg to 15 mg per day, which may be taken as a single daily dose. Therapy should be continued for at least six months and up to 18 months. Serial thyroid function monitoring is recommended, together with appropriate dosage modification in order to maintain a euthyroid state.

Blocking-replacement regimen: dosage is maintained at the initial level, i.e. 20 mg to 60 mg per day, and supplemental L-thyroxine, 50 mcg to 150 mcg per day, is administered concomitantly, in order to prevent hypothyroidism. Therapy should be continued for at least six months and up to 18 months. Where a single dosage of less than 20 mg is recommended, it is intended that carbimazole 5 mg tablets should be taken.

Method of administration

Oral

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in 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.

## 4.4 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.

Rare cases of pancytopenia/aplastic anaemia and isolated thrombocytopenia have also been reported. Additionally, very rare 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 the drug 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.

Following the onset of any signs and symptoms of hepatic disorder (pain in the upper abdomen, anorexia, general pruritus) in patients, the drug should be stopped and liver function tests performed immediately. Early withdrawal of the drug will increase the chance of complete recovery.

Carbimazole tablets 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.

Carbimazole 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 carbimazole.

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 carbimazole. Tracheal obstruction may occur due to intrathoracic goitre.

The use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section 4.6).

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

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.

Women of childbearing potential and pregnancy

Women of childbearing potential have to use effective contraceptive measures during treatment.

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).

Carbimazole contains lactose

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Little is known about interactions.

Interaction studies have not been performed in paediatric patients.

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

Since carbimazole is a vitamin K antagonist, the effect of anticoagulants could be intensified. Additional monitoring of 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 medications without reducing the theophylline dosage.

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

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

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.

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.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Carbimazole 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. 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, cases of congenital malformations have been observed following the use of carbimazole or its active metabolite methimazole during pregnancy.

A causal relationship of these malformations, especially choanal atresia and aplasia cutis congenita (congenital scalp defects), to transplacental exposure to carbimazole and methimazole cannot be excluded.

Therefore the use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section 4.4).

Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. Therefore, carbimazole should be used in pregnancy only when propylthiouracil is not suitable.

If carbimazole is used in pregnancy, the dose must be regulated by the patient's clinical condition. The lowest dose possible should be used, and this can often be discontinued three or four weeks before term, in order to reduce the risk of neonatal complications.

The blocking-replacement regimen should not be used during pregnancy since very little thyroxine crosses the placenta in the last trimester.

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).

Breast-feeding

Carbimazole is excreted in milk and if treatment is continued during lactation the patient should not continue to breast-feed her baby.

Women of childbearing potential

Women of childbearing potential have to use effective contraceptive measures during treatment (see section 4.4).

## 4.7 Effects on ability to drive and use machines

Not relevant.

## 4.8 Undesirable effects

Adverse reactions usually occur in the first eight weeks of treatment. The most common 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 drug.

The undesirable effects are listed below by system organ class and the following frequency convention: Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Bone marrow depression including neutropenia, eosinophilia, leucopenia and agranulocytosis has been reported. Fatalities with carbimazole-induced agranulocytosis have been reported. Rare cases of pancytopenia/aplastic anaemia and isolated thrombocytopenia have also been reported. Additionally, very rare 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 the drug 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.

Generalised lymphadenopathy.

Immune system disorders

Angioedema and multi-system hypersensitivity reactions such as cutaneous vasculitis, liver, lung and renal effects occur.

Endocrine disorders

Insulin autoimmune syndrome (with pronounced decline in blood glucose level).

Nervous system disorders

Headache, neuritis, polyneuropathy.

Vascular disorders

Bleeding.

Gastrointestinal disorders

Nausea, mild gastrointestinal disturbance.

Loss of sense of taste has been observed.

Acute salivary gland swelling.

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 tablets should be withdrawn.

Skin and subcutaneous tissue disorders

Skin rashes, pruritus, urticaria. Hair loss has been occasionally reported.

Severe cutaneous hypersensitivity reactions have been reported in both adult and paediatric patients, including Stevens-Johnson syndrome (very rare including isolated reports: severe forms, including generalised dermatitis, have only been described in isolated cases).

Musculoskeletal and connective tissue disorders

Isolated cases of myopathy have been reported. Patients experiencing myalgia after the intake of carbimazole should have their creatine phosphokinase levels monitored

General disorders and administration site conditions

Fever, malaise.

Injury, poisoning and procedural complications

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 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, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

Symptoms

No symptoms are likely from a single large dose.

Treatment

No specific treatment is indicated.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC Code: H03B B

Pharmacotherapeutic group: Sulfur-containing imidazole derivatives

Mechanism of action:

Carbimazole, a thionamide, is a pro-drug which undergoes rapid and virtually complete metabolism to the active metabolite, thiamazole, also known as methimazole. The method of action is believed to be inhibition of the organification of iodide and the coupling of iodothyronine residues which in turn suppress the synthesis of thyroid hormones.

## 5.2 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 0.51/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.

## 5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Anhydrous lactose

Croscarmellose sodium

Magnesium stearate

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Do not store above 25°C.

Store in the original packaging in order to protect from light.

## 6.5 Nature and contents of container

Blister pack:

PVC/PVdC/PE blisters with aluminum foil in packs of 10, 20, 14, 28, 30, 50, 56, 60, 84, 90, 100 & 112 Tablets (Not all pack sizes will be marketed).

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements.

# 7 MARKETING AUTHORISATION HOLDER

Cygnus Pharma Limited

72 Cardigan Street

Luton, LU1 1RR,

United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 49255/0011

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/11/2020

## 10 DATE OF REVISION OF THE TEXT

20/11/2020