SCHEDULING STATUS

S3

1 NAME OF THE MEDICINAL PRODUCT

CARBIFORA 5 (5 mg tablets)

CARBIFORA 20 (20 mg tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CARBIFORA 5 (5 mg tablets): Each tablet contains 5 mg carbimazole.

CARBIFORA 20 (20 mg tablets): Each tablet contains 20 mg carbimazole.

Contains sugar: lactose anhydrous 70 mg (CARBIFORA 5) & 280 mg (CARBIFORA 20).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White coloured, round shaped, uncoated tablet plain on one side and break line on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CARBIFORA is indicated for the management of hyperthyroidism, thyrotoxicosis (including thyroid storm), and also for the preparation of patients for thyroidectomy.

CARBIFORA tablets can also be used for therapy prior to and post radio-active ablative therapy.

4.2 Posology and method of administration

Adults

CARBIFORA 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 administration

4.3 Contraindications

CARBIFORA is contraindicated in:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Serious, pre-existing haematological conditions, such as agranulocytosis. Fatalities with PN-induced agranulocytosis have been reported (see sections 4.4 and 4.8)
- Severe hepatic insufficiency.

- Patients with a history of acute pancreatitis after administration of carbimazole or it's active metabolite thiamazole.
- Use with other thiourea antithyroid medicines.
- Pregnancy and lactation and in women intending to become pregnant (see section 4.6).
- Carbimazole should be given with the utmost caution, or not at all, if there is any degree of tracheal obstruction, as high dosages may produce thyroid enlargement and obstructive symptoms may become marked.

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.

Patients should be warned to report the incidence of mouth ulcers or sore throat, bruising or bleeding, malaise or fever, as they may precede abnormal findings in the blood by several days and should be instructed to stop the CARBIFORA and seek medical advice immediately. In such patients, blood cell counts should be performed immediately, particularly where there is any clinical evidence of infection. Treatment should be discontinued if there is any clinical or laboratory evidence of neutropenia.

Following the onset of any signs and symptoms of hepatic disorder (pain in the upper abdomen, anorexia, general pruritus) in patients, CARBIFORA should be stopped and

liver function tests performed immediately. Early withdrawal of the medicine will increase the chance of complete recovery.

CARBIFORA 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.

CARBIFORA should be temporarily stopped at the time of administration of radiation (to avoid thyroid crisis).

Patients experiencing myalgia after the intake of CARBIFORA should have their creatine phosphokinase levels monitored.

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

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

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 CARBIFORA. Tracheal obstruction may occur due to intrathoracic goitre.

Thyroid function must be checked before the initiation of therapy and regularly thereafter.

The use of CARBIFORA 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.

It is recommended to increase the precautions with regard to use of CARBIFORA in non-compliant patients, patients who are confused or have poor memory, and patients with galactose intolerance.

CARBIFORA 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 medicines and other forms of interaction

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

Since CARBIFORA 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 CARBIFORA may result in increased clearance of prednisolone.

CARBIFORA 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:

CARBIFORA may decrease thyroidal uptake of sodium iodide I 123 or I 131, or pertechnetate, withdrawal of CARBIFORA 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception and not plan to become pregnant when treated with CARBIFORA.

Pregnancy

Safety in pregnancy and lactation has not been established. CARBIFORA may cause foetal or neonatal hypothyroidism and goitre. CARBIFORA 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 CARBIFORA or its active metabolite methimazole during pregnancy. A causal

relationship of these malformations, especially choanal atresia and aplasia cutis congenital, to transplacental exposure to CARBIFORA and methimazole cannot be excluded. Therefore, the use of CARBIFORA 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.

Breastfeeding

Carbimazole is secreted in breast milk and, if treatment is continued during lactation, the patient should not continue to breastfeed her baby.

4.7 Effects on ability to drive and use machines

CARBIFORA has no effect on the ability to drive or use machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions usually occur in the first eight weeks of treatment. The most frequently occurring reactions are nausea, headache, arthralgia, mild gastric distress, skin rashes and pruritus. These reactions are usually self-limiting and may not require withdrawal of the medicine.

b. Tabulated summary of the adverse effects

MedDRA System Organ Classification (SOC) according to the sequence:	**Adverse Reaction**	**Frequency**
Blood and lymphatic system disorders	Bone-marrow depression including neutropenia, eosinophilia, leucopenia and agranulocytosis, generalised lymphadenopathy	Less frequent
	pancytopenia/aplastic anaemia and isolated thrombocytopenia haemolytic anaemia	Frequency not known
Immune system disorders	angioedema; multi-system hypersensitivity reactions such as cutaneous vasculitis, liver, lung and renal effects occur	Less frequent
Endocrine disorders	insulin autoimmune syndrome (with pronounced decline in blood glucose level).	Frequency not known
Nervous system disorders	headache	Frequent

	neuritis, polyneuropathy; paraesthesias	Frequency not known
Vascular disorders	vasculitis, bleeding	Frequency not known
Gastrointestinal disorders	nausea, mild gastrointestinal disturbance.	Frequent
	loss of sense of taste has been observed. Acute salivary gland swelling, Acute pancreatitis.	Frequency not known
Hepatobiliary disorders	hepatic disorders, including abnormal liver function tests, hepatitis, cholestatic hepatitis, cholestatic jaundice and most commonly jaundice (see section c)	Frequency not known
Skin and subcutaneous tissue disorders	skin rashes, pruritus, urticaria, skin pigmentation.	Frequent
	severe cutaneous hypersensitivity reactions including Stevens-Johnson syndrome, generalised dermatitis (see section c)	Less frequent
	hair loss	Frequency not known

Musculoskeletal and connective tissue disorders	myopathy, arthralgia, myalgia	Less frequent
	lupus-like syndrome (see section c)	Frequency not known
Renal and urinary disorders	nephritis	Frequency not known
General disorders and administration site conditions	fever, malaise	Frequency not known
Injury, poisoning and procedural complications	bruising	Frequency not known

c. Description of selected adverse reactions

The most severe adverse reactions are described below:

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.

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 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.

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

Severe cutaneous hypersensitivity reactions have been reported in both adult and paediatric patients, including Stevens-Johnson syndrome (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.

d. Paediatric population

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

e. Other special populations

Special consideration is to be given to Women of childbearing potential and pregnancy (see section 4.6). It has been reported that the risk of a fatal outcome to neutrophil dyscrasia may be greater in the elderly (aged 65 or over) (see section 4.4).

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

Overdosage or accidental poisoning may result in hypothyroidism and goitre. If blood dyscrasias occur, the medicines should be immediately withdrawn.

Treatment

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Medicine Class: A 21.12 Hormone inhibitors

Pharmacotherapeutic group: Sulfur-containing imidazole derivatives; ATC code: H03BB01

Mechanism of action

Carbimazole is an anti-thyroid substance 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.

5.2 Pharmacokinetic properties

Absorption

Carbimazole is absorbed rapidly from the gastrointestinal tract and is widely distributed throughout the body. Carbimazole is rapidly metabolised to thiamazole. After oral ingestion, peak plasma concentrations of thiamazole, the active moiety, occur at 1 to 2 hours.

Distribution

Carbimazole readily crosses the placental barrier and also attains a high concentration in the milk of lactating patients. The total volume of distribution of thiamazole is 0.5 1/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

6.1 List of excipients

Lactose Anhydrous, croscarmellose sodium, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Multiple blisters may be packed in a vanished, printed cardboard carton (10 tablets packed in a blister made of plain aluminium foil and white PVC/PE/PVDC).

Keep the blisters in the carton until required for use.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia,

1827

8 REGISTRATION NUMBER

CARBIFORA 5: 56/21.12/1133.1131

CARBIFORA 20: 56/21.12/1134.1132

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 January 2025

10 DATE OF REVISION OF THE TEXT