

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NeoMercazole 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NeoMercazole 20 mg tablet contains carbimazole 20 mg.

Excipients with known effect:

Lactose monohydrate (20.0 mg/tablet)

Sucrose (131.74 mg/tablet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pink, circular biconvex tablet, imprinted with "Neo 20" on the obverse and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

NeoMercazole 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

Posology

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

Adults

The initial dose is in the range 20 – 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 – 15 mg per day, which may be taken as a single daily dose. Therapy should be continued for at least six, and up to eighteen months.

Serial thyroid function 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 – 60 mg per day, and supplemental l-thyroxine, 50 – 150 mcg per day, is administered concomitantly, in order to prevent hypothyroidism. Therapy should be continued for at least six months, and up to eighteen months.

Where a single dosage of less than 20 mg is recommended, it is intended that NeoMercazole 5 mg Tablets should be taken.

Elderly

No special dosage regimen is required, but care should be taken to observe the contra- indications 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 and over).

Paediatric population

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

Initial dosage for the treatment of children and adolescents above 3 years of age should be adjusted to the body weight of the patients. Usually treatment is initiated at a daily dose of 0.5 mg/kg, divided into two or three equal doses. For maintenance therapy, the daily dose can be reduced depending on the response of the patient to the treatment. Additional treatment with levothyroxine may be required to avoid hypothyroidism. A total daily dose of 40 mg carbimazole should not be exceeded.

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.

Method of administration

Oral

4.3 Contraindications

NeoMercazole is contraindicated in patients with:

- 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 purpura, anaemia, 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.

NeoMercazole 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 liver disorder.

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

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

NeoMercazole should be stopped temporarily at the time of administration of radio-iodine, to avoid thyroid crisis.

Precaution should be taken in patients with intrathoracic goitre, which may worsen during initial treatment with NeoMercazole. 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 risk of cross-allergy between carbimazole, thiamazole 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).

NeoMercazole contains lactose.

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

NeoMercazole contains sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-iso maltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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

4.6 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

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, very rare 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 congenital (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 NeoMercazole is used in pregnancy the dose of NeoMercazole must be regulated by the patient's clinical condition. The lowest dose possible should be used, and this can often be discontinued three to 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.

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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

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

Fertility

No fertility data available.

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 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 drug.

The undesirable effects are listed below by system organ class and the following frequency convention:

Rare ($\geq 1/10,000$ to $< 1/1,000$),

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse events
Blood and lymphatic system disorders	Rare	Purpura, anaemia, pancytopenia/aplastic anaemia, neutropenia, leucopenia and isolated

		thrombocytopenia have also been reported.
	Very rare	Haemolytic anaemia
	Not known	Bone-marrow failure, including neutropenia and agranulocytosis have been reported. Lymphadenopathy
Immune system disorders	Not known	Angioedema and multiorgan hypersensitivity reactions, such as cutaneous vasculitis, liver, lung and renal effects occur
Endocrine disorders	Not known	Insulin autoimmune syndrome (with pronounced decline in blood glucose levels)
Nervous system disorders	Not known	Headache, neuritis, polyneuropathy
Vascular disorders	Not known	Haemorrhage
Gastrointestinal system disorders	Not known	Pancreatitis acute, nausea, mild gastric disorders. ageusia , acute salivary gland swelling,
Hepatobiliary disorders	Not known	Hepatic disorders, including abnormal liver function tests, hepatitis, cholestatic hepatitis, cholestatic jaundice and most commonly jaundice, have been reported*.
Skin and subcutaneous tissue disorders	Very rare	Severe cutaneous hypersensitivity reactions in both adult and paediatric patients, including Stevens-Johnsons syndrome**.
	Not known	Skin rash, pruritus, urticaria. Alopecia.
Musculoskeletal and connective tissue disorders	Not known	Patients experiencing myalgia after the intake of NeoMercazole should have their creatine phosphokinase levels monitored. Isolated cases of myopathy have been reported.
General disorders and administration site conditions	Not known	Pyrexia, malaise
Injury, poisoning and procedural complications	Not known	Contusion

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, blood cell counts should be performed, particularly where there is any clinical evidence of infection.

* in these cases, carbimazole should be withdrawn.

** very rare including isolated reports: severe forms, including generalised dermatitis, have only been

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

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Symptoms

No symptoms are likely from a single large dose.

Management

No specific treatment is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulfur-containing imidazole derivatives

ATC Code: H03B B01

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 0.5 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.

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

Lactose monohydrate
Starch maize
Gelatin
Magnesium stearate
Sucrose
Acacia
Talc
Red Iron oxide E172
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

NeoMercazole 20mg tablets are available in HDPE bottles with a low density polyethylene tamper evident snap-fit closure or a round polypropylene, white tamper-evident screw cap with integrated desiccant. Each bottle contains 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 1995

Date of last renewal: 13 March 2010

10 DATE OF REVISION OF THE TEXT

January 2021