1 NEO-MERCAZOLE

Carbimazole 5mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg of carbimazole.

Excipients with known effect:

Sucrose
Lactose

For a full list of excipients see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

A pale pink tablet, shallow bi-convex tablet with a white centrally located core, one face plain, with Neo 5 imprinted on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary thyrotoxicosis, even in pregnancy.

Secondary thyrotoxicosis - toxic nodular goitre.

However, Neo-Mercazole really has three principal applications in the therapy of hyperthyroidism:

1. Definitive therapy - induction of a permanent remission.
2. Preparation for thyroidectomy.
3. Before and after radio-active iodine treatment.

4.2 Dose and method of administration

Neo-Mercazole should only be administered if hyperthyroidism has been confirmed by laboratory tests.

Adults

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

The usual initial dosage for adults is 60 mg per day given in divided doses. Thus:

Mild cases	20 mg	Daily in divided dosage
Moderate cases	40 mg	
Severe cases	40-60 mg	

The initial dose should be titrated against thyroid function until the patient is euthyroid in order to reduce the risk of over-treatment and resultant hypothyroidism.

Three factors determine the time that elapses before a response is apparent:

(a) The quantity of hormone stored in the gland.
(Exhaustion of these stores usually takes about a fortnight).
(b) The gland secretory rate.
(c) The degree of inhibition of hormone synthesis achieved by Neo-Mercazole.

If large stores of hormone are present, as in nodular goitre, response to Neo-Mercazole 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 which may be taken as a single daily dose.

Experience has shown there is a wide variation of sensitivity to the medicine and from time to time in a particular patient. For this reason patients should be seen monthly for the first year; and thereafter at three or six-monthly intervals.

Serial thyroid function monitoring is recommended, together with appropriate dosage modification in order to maintain a euthyroid state.

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).

Children
The usual initial daily dose is 15 mg per day.

Duration of therapy
First, the time required to render a patient euthyroid depends very much on the type of case being treated. Toxic nodular goitres usually take very much longer.

Second, once a remission has been secured maintenance dosage should be continued for at least twelve months, and up to two years of Neo-Mercazole treatment may be required.

Of course, if thyroidectomy is intended, it can be carried out once the euthyroid state is

achieved with Neo-Mercazole, which is then discontinued.

Change-over from thiouracils
When treatment with one of the thiouracils is replaced by Neo-Mercazole therapy, one 50 mg tablet of methylthiouracil or propylthiouracil can be taken as equivalent to one 5 mg tablet of Neo-Mercazole.

Delayed response to therapy
If no relief is obtained within three months, the possible causes are:
(a) Patients have failed to take their Neo-Mercazole. This is the most common cause.
(b) Previous iodine therapy which has resulted in an increased hormone store within the gland.
(c) Inadequate dosage of Neo-Mercazole.

Preparation of thyrotoxic patients for surgery
Neo-Mercazole is prescribed prior to thyroidectomy, and should then be given in sufficient dosage for long enough to render the patient euthyroid.

4.3 Contraindications

Neo-Mercazole is contraindicated in patients with:
• A previous history of adverse reactions to Neo-Mercazole or to any of the excipients in the composition
• Serious, pre-existing haematological conditions in particular granulocytopenia.
• Simple goitre.
• Severe hepatic insufficiency and liver failure Retrosternal goitre and when signs of tracheal compression are present.
• A history of acute pancreatitis after administration of carbimazole or its active metabolite thiamazaole.

4.4 Special warnings and precautions for use

Neo-Mercazole should only be administered if hyperthyroidism has been confirmed by laboratory tests.
Treatment with Neo-Mercazole is associated with a risk of inhibiting haematopoiesis (leukopenia, granulocytopenia, agranulocytosis, aplastic anaemia, and thrombocytopenia) and of liver damage. As fatal cases of agranulocytosis and very rare cases of haemolytic anaemia with Neo-Mercazole have been reported and early treatment of agranulocytosis is essential, it is important that patients should always be warned about the onset of angina, sore throats, bruising or bleeding, mouth ulcers, fever, malaise, stomatitis, furunculosis or any other infections and should be instructed to stop the drug and to seek medical advice immediately. In such patients, in particular following doses of over 40 mg/day, in patients aged over 40, and within the first two months of treatment blood cell counts of leucocytes and granulocytes should be performed immediately before starting treatment and once a week during the first six weeks of treatment, particularly where there is any clinical evidence

of infection. The development of bone-marrow depression is reversible if the drug is discontinued early. Early withdrawal of Neo-Mercazole will increase the chance of complete recovery.

Special precaution is recommended in the case of concurrent administration of medicinal products capable of inducing agranulocytosis.

Since thyroid hormones can alter the amount of vitamin K-dependent clotting factors and thus the extent of inhibition by oral anticoagulants, careful control of anticoagulant dosage is required as hyperthyroid patients receiving treatment with Neo-Mercazole are rendered euthyroid; additional monitoring of PT/INR should be considered, especially before surgical procedures. Ne-Mercazole administration can itself, rarely, result in hypoprothrombinaemia, which may increase the risk of haemorrhagic events.

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.

Neo-Mercazole 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.

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

Iodine-induced hyperthyroidism is not an indication for Neo-Mercazole.

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

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

Neo-Mercazole contains lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

Neo-mercazole contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Control of thyroxine in serum is necessary. Precaution should be taken in patients with intrathoracic goitre, which may worsen during initial treatment with Neo-Mercazole. Tracheal obstruction may occur due to intrathoracic goitre.

Patients experiencing myalgia after the intake of Neo-Mercazole should have their creatine phosphokinase levels monitored.

Should the volume of the goitre increase, the dose of Neo-Mercazole should not be increased, since growth in volume is more likely to occur following overdosing of the preparation.

There is a risk of cross-allergy between Neo-Mercazole, 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 Neo-Mercazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see section 4.6 Fertility, pregnancy and lactation).

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, fetal and neonatal monitoring is warranted (see section 4.6 Fertility, pregnancy and lactation).

4.5 Interaction with other medicines and other forms of interaction

Little is known about interactions.

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 and due to the extent of inhibition by oral anticoagulants, careful control of anticoagulant dosage is required as hyperthyroid patients receiving treatment with Neo-Mercazole are rendered euthyroid; additional monitoring of PT/INR should be considered, especially before surgical procedures. Neo-Mercazole administration can itself, rarely, result in hypoprothrombinaemia, which may increase the risk of haemorrhagic events.

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 Neo-Mercazole may result in increased clearance of prednisolone.

Neo-Mercazole 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.

Iodine deficiency will increase the response to Neo-Mercazole while an excess of iodine will attenuate it. The effect of Neo-Mercazole is reduced if the patient has undergone iodine treatment.

Drug and laboratory interactions

Hypoprothrombinaemia and bleeding may be caused hence, prothrombin time should be monitored during therapy with the drug, especially before surgical procedures.

4.6 Fertility, pregnancy and lactation

Category C

Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and fetal complications. Carbimazole and its active metabolite are able to cross the placenta which may cause foetal hypothyroidism and thyroid hyperplasia 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.

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. Congenital malformations are greater in the children of mothers whose hyperthyroidism has remained untreated than in those to whom treatment with Neo-Mercazole has been given. However, very rare cases of congenital malformations have been observed following the use of Neo-Mercazole or its active metabolite methimazole during pregnancy. A causal relationship between these malformations, especially craniofacial malformations (choanal atresia, facial dysmorphism), exomphalos, oesophageal atresia, aplasia cutis congenita (congenital scalp defects), omphalo-mesenteric duct anomaly, ventricular septal defect, transplacental and diplacental exposure to Neo-Mercazole and methimazole cannot be excluded.

In humans, the foetal thyroid gland begins to trap iodine 10-12 weeks after conception. Transient thyroid function abnormalities have been reported in new-borns born to mothers treated with Neo-Mercazole during pregnancy. 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, fetal and neonatal monitoring is recommended (see section 4.4 Special warnings and precautions for use).

Cases of renal, skull, cardiovascular congenital defects, exomphalos, gastrointestinal malformation, umbilical malformation and duodenal atresia have also been reported. There is clear evidence of a risk for the unborn child (development of goitre or of cretinism). Graves' disease occurs in about 0.05 to 0.2% of pregnant women. Hyperthyroidism of the foetus leads to miscarriages or to premature birth in 20% of cases, and the number of stillbirths among cases of hypertrophy of the thyroid gland is considerable. There is an increased risk of premature craniosynostosis. The possibility of replacing Neo-Mercazole with propylthiouracil should furthermore be taken into consideration, since this antithyroid drug has not resulted so far in any thyroid modifications at all in the unborn child. Some authors prefer surgical treatment. Therefore, Neo-Mercazole should be used in pregnancy only when propylthiouracil is not suitable. If a pregnant woman takes Neo-Mercazole or a female patient becomes pregnant during treatment, they must be informed of the possible risks for the unborn child and the dose of Neo-Mercazole must be regulated by the patient's clinical condition to achieve a normal thyroid function for the mother, but without causing hypothyroidism of the foetus. In such cases, particularly careful monitoring is required in weeks 10 to 14 of pregnancy due to the fact that the foetus will start to produce the hormone in this period. The thyroid gland of the foetus does not start to develop until week 11 of pregnancy and only becomes functional around week 18. Treatment can therefore be continued until the third month. 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 and hypothyroidism precisely at a time when the brain of the foetus will be growing most. The posologies will need to be adjusted to obtain normal thyroid function or mild maternal hyperthyroidism in order to limit the risk of foetal hypothyroidism. Maternal supplementation with L-thyroxine, T3 and T4 in order to prevent foetal hypothyroidism is a controversial issue and might prove ineffective for the foetus because it barely crosses the placenta. The blocking-replacement regimen should not be used during pregnancy since very little thyroxine crosses the placenta in the last trimester.

A prenatal exam (ultrasound) should be considered in order to detect some of the above-cited malformations and to monitor the foetal thyroid gland. A neonatal thyroid function test should be performed.

Neo-Mercazole and its active metabolite are secreted in breast milk and, and due to the risk of neonatal hypothyroidism and agranulocytosis at high doses if treatment is continued during lactation, the patient should not continue to breast-feed her baby or switch to treatment with propylthiouracil, since the latter passes into breast milk about ten times less freely than does thiamazole. Breast-feeding can be carried out if the infant's thyroid function is monitored.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In the event of an increase in goitre volume, hypothyroidism by overdose should firstly be suspected.
Adverse reactions usually occur in the first eight weeks of treatment. The most frequently occurring reactions are nausea, headache, arthralgia (especially in the joint of the thumb), mild gastric distress, skin rashes, urticaria and pruritus. These reactions are usually self-limiting and may not require withdrawal of the medicine.

Infections and infestations

Not known: Furuncle, sialoadenitis

Blood and lymphatic system disorders

Rare: Pancytopenia/aplastic anaemia, isolated thrombocytopenia, Hypoprothrombinaemia

Very rare: Haemolytic anaemia

Not known: Bone marrow failure including neutropenia, eosinophilia, leukopenia, agranulocytosis, bone-marrow aplasia, Fatalities with Neo-Mercazole-induced agranulocytosis have been reported, generalized lymphadenopathy.

Patients should always be warned about the onset of sore throats, bruising or bleeding, mouth ulcers, fever, malaise 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.

Immune system disorders

Not known: Angioedema and multi-system hypersensitivity reactions such as cutaneous vasculitis, liver, lung and renal effects occur.

Endocrine disorders

Not known: Hypoglycemic episodes due to Insulin autoimmune syndrome (with pronounced decline in blood glucose level) which could even lead to hypoglycemic shock.

Nervous system disorders

Common: Headache, Dizziness, paraesthesia

Not known: Neuritis, Polyneuropathy, Brain disorder not otherwise specified (NOS), Ageusia,

Vascular Disorders

Not Known: Haemorrhage

Gastro-intestinal system disorders

Not known: Nausea, mild dyspepsia, stomatitis, abdominal pain, acute pancreatitis

Hepato-biliary system disorders

Most common: Jaundice may persist for several weeks after discontinuation of the treatment.

Rare: Hepatic necrosis

Not known: Liver disorder, including liver function tests abnormal, hepatitis, hepatitis cholestatic, jaundice cholestatic have been reported; in these cases Neo-Mercazole should be withdrawn.

Skin and subcutaneous tissue disorders

Very rare: 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)

Not known: Rash, pruritis, urticaria. Alopecia has been occasionally reported. Pigmentation disorder, erythema

Musculoskeletal system and connective tissue disorders

Isolated cases: Myopathy have been reported.

Patients experiencing myalgia after the intake of Neo-Mercazole should have their creatine phosphokinase levels monitored.

Not known: Arthralgia (especially in the joint of the thumb)

General disorders and administration site conditions

Not known: Fever, Malaise, Exhaustion

Injury, poisoning and procedural complications

Not known: Bruising

Investigations

Not known: Liver function test abnormal

Potential effects on laboratory test results

Hypoprothrombinaemia and bleeding may be caused hence, prothrombin time should be monitored during therapy with the drug, especially before surgical procedures.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Over dosage with no hormone replacement will cause the side effects to worsen and lead to hypothyroidism with elevated TSH and goitre enlargement. No symptoms are likely from a single large dose, and so no specific treatment is indicated.

In case of manifest overdosing, the treatment must be discontinued and, if necessary, the symptoms treated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-thyroid agent. ATC Code: H03B B01

Mechanism of action:
Carbimazole is a synthetic antithyroid drug that is metabolized into methimazole (thiamazole), which has a prolonged antithyroid effect. Carbimazole, a thionamide, is a pro-drug which undergoes rapid and virtually complete metabolism to the active metabolite, thiamazole. Taken orally, carbimazole blocks thyroid hormonogenesis by inhibiting the action of thyroid peroxidase, organification of iodide and their uptake by tyrosyl radicals as well as the coupling of iodotyrosines with iodothyronine residues (T_3 and T_4) which in turn suppress the synthesis of thyroid hormones. It causes a hypersecretion of TSH.

Alongside these two effects, both typical of all synthetic antithyroid agents, carbimazole also has another particular property: It blocks the enzyme dehalogenase, which enables recovery of any organic iodine that has not been distributed. Intrathyroid iodine is thus gradually eliminated, leading to iodine avidity in the thyroid gland. This means that it is always possible to replace radioactive iodine treatment with carbimazole.

5.2 Pharmacokinetic properties

<u>Absorption</u>
About 90-100% of Carbimazole is rapidly absorbed in the intestines within 15-30 minutes and is rapidly metabolised to its active metabolite methimazole that can be only identified in the blood. The mean peak plasma concentration of methimazole is reported to occur one hour after a single dose of carbimazole. After oral ingestion, peak plasma concentrations of 0.2 to 1.0 µg/l methimazole, the active moiety, are reached within 1 to 2 hours following administration of a dose of 60 mg.

<u>Distribution</u>
The blood half-life ranges from 4-12 hours depending on the person. This variability seems more related to individual variability than to thyroid status per se. Distribution volume is approximately 40 litres and the total volume of distribution of methimazole is 0.5L/kg and it

binds with plasma proteins up to 40%. Methimazole is concentrated in the thyroid gland rapidly after administration which has the effect of prolonging the activity of carbimazole.

Metabolism

Carbimazole is hydrolysed rapidly, but not absolutely completely, to the active metabolite methimazole in the blood by hydrolysis and enzymatic decarboxylation. It undergoes oxidative decomposition in the liver and in the thyroid. Carbimazole has a half-life of 5.3 to 5.4 hours. The apparent plasma half-life of methimazole is reported as 6.4 hours is longer in the thyroid gland (for about 20 hours) which corresponds to the duration of the effect of a single dose. However, methimazole 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. It is possible that the plasma half-life may also be prolonged by renal or hepatic disease. Methimazole 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 methimazole or its metabolites. The remainder appears in faeces. There is 10% enterohepatic circulation. Approximately 7% of methimazole is excreted unchanged.

Kinetics in special patient groups

The plasma half-life is longer in patients with disorders of the liver or kidney functions

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 datasheet

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acacia
Gelatin
Ferric oxide
Lactose
Magnesium stearate
Maize starch
Purified talc
Sucrose

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C

6.5 Nature and contents of container

Neo-Mercazole 5mg tablets are available in HDPE containers with an LDPE closure. Each bottle contains 100 tablets.

6.6 Special precautions for disposal

No special precautions

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

AFT Pharmaceuticals Ltd
PO Box 33.203
Takapuna
Auckland
Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

31/12/1969

10 DATE OF REVISION OF THE TEXT

21 August 2019

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
November 2018	All	Reformat consistent with new Medsafe Data Sheet Template.
August 2019	4.3, 4.4 and 4.8	Addition of contraindication, precautions and adverse effect related to pancreatitis from the PRAC recommendation.
August 2019	4.4 and 4.6	Addition of precautions and warnings (new information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy) from the MARC recommendation due to evidence of congenital malformations when administered during pregnancy.