

PRODUCT INFORMATION

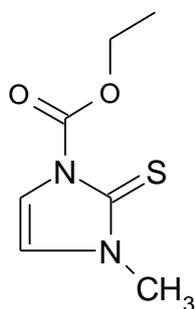
NEO-MERCAZOLE (carbimazole) 5 mg tablet

NAME OF THE MEDICINE

Carbimazole

The chemical name for carbimazole is ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate. The molecular formula is C₇H₁₀N₂O₂S. The molecular weight is 186.2.

Chemical structure:



CAS Registry Number: 22232-54-8

DESCRIPTION

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

NEO-MERCAZOLE is available as a pink tablet containing the following excipients: lactose, sucrose, maize starch, magnesium stearate, purified talc, acacia, iron oxide red and gelatin.

PHARMACOLOGY

Pharmacodynamics

NEO-MERCAZOLE is an anti-thyroid agent.

NEO-MERCAZOLE 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 NEO-MERCAZOLE, and also in preparation of patients for operation.

Pharmacokinetics

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.

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.

CONTRAINDICATIONS

- NEO-MERCAZOLE 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.

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

PRECAUTIONS

NEO-MERCAZOLE 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 **DOSAGE AND ADMINISTRATION**).

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.

Rare cases of pancytopenia/aplastic anaemia, and very rare cases of haemolytic anaemia and thrombocytopenia have been reported (see **ADVERSE EFFECTS**).

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.

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.

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.

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

Precautions 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.

The use of carbimazole in non-pregnant women of childbearing potential should be based on individual risk/benefit assessment (see **PRECAUTIONS, Use in pregnancy**).

Effects on fertility

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

Use in pregnancy (Category C)

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 **PRECAUTIONS**).

The basal metabolic rate is raised during pregnancy and the dosage of NEO-MERCAZOLE 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.

NEO-MERCAZOLE 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.

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.

Carcinogenicity and mutagenicity

There is no information on carcinogenicity or mutagenicity following treatment with carbimazole.

INTERACTIONS WITH OTHER MEDICINES

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

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.

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 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.

Interaction studies have not been performed in paediatric patients.

ADVERSE 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, < 1/1000
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 **PRECAUTIONS**).

Immune system disorders

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

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.

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.

DOSAGE AND 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.

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 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.

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 NEO-MERCAZOLE, which is then discontinued.

Changeover from thiouracils

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

Delayed response to NEO-MERCAZOLE therapy

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

OVERDOSAGE

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 Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

NEO-MERCAZOLE 5 mg is available for oral administration as a pale pink, circular biconvex tablet embossed with Neo 5 on one side and plain on the other side.

NEO-MERCAZOLE is available in a bottle of 100 tablets.

Store below 25°C. Protect from moisture.

NAME AND ADDRESS OF THE SPONSOR

Amdipharm Mercury (Australia) Pty Ltd
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North Sydney NSW 2060

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine – Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

23 May 2012

DATE OF MOST RECENT AMENDMENT

01 February 2017

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