Thyrozol®
Thiamazole

Antithyroid

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Thyrozol 5 mg film-coated tablet contains 5 mg Thiamazole.
Each Thyrozol 10 mg film-coated tablet contains 10 mg Thiamazole.

Excipient(s):
Contains 200 mg Lactose monohydrate per tablet (Thyrozol 5 mg), see section 3.4 Special Warnings and Special Precautions for Use.
Contains 195 mg Lactose monohydrate per tablet (Thyrozol 10 mg), see section 3.4 Special Warnings and Special Precautions for Use.

For a full list of excipients, see section 5.1 List of Excipient.

2. PHARMACEUTICAL FORM
Film-coated tablet.

3. CLINICAL PARTICULARS
3.1 Indications
- Drug treatment of hyperthyroidism, especially in slight or absent thyroid enlargement (goitre) as well as in younger patients.
- Preparation for surgery in all forms of hyperthyroidism.
- Preparation of patients with hyperthyroidism for planned radioiodine treatment to prevent the risk of a thyrotoxic crisis after therapy.

3.2 Posology and Method of Administration
Conservative Treatment of Hyperthyroidism
Two different dosage regimens are recommended:
a) Complete blocking of thyroid hormone production is achieved with daily doses of 25 to at the most 40 mg Thiamazole.
   Initial therapy (to achieve normal metabolic activity of the thyroid gland):
   Maximum daily dose: 40 mg Thiamazole in single doses of maximally 20 mg Thiamazole, depending on the severity of the disease.
   2 times 1 tablet Thyrozol 10 mg (20 mg) - mild cases
   2 times 1 tablet Thyrozol 20 mg (40 mg) - severe cases.
   After normalization of the thyroid function (generally between weeks 3 and 8) the dose is stepwise reduced in long-term treatment to a maintenance dose of 5 to 20 mg daily. This dosage usually requires the additional administration of thyroid hormones.
b) In therapy with Thyrozol alone the dose depends on metabolic activity which must be checked individually in each patient, paying particular attention to the TSH (= Thyroid Stimulating Hormone)

DISETUJUI OLEH BPOM: 31/12/2021

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values. The dose is in this case between 2.5 and 10 mg per day.
Iodine-induced hyperthyroidism may possibly require higher doses.

In conservative treatment of hyperthyroidism therapy with Thyrozol is usually continued over a period of 6 months to 2 years (1 year on average). Statistically, the probability of remission increases with the duration of therapy.

When used in preparing patients with autonomous adenoma or latent hyperthyroidism for a required exposure to iodine, the duration of treatment with Thyrozol depends on the time the iodine-containing substance is retained in the body.

Patients with considerably enlarged thyroid glands and constriction of the trachea should only undergo short-term treatment with Thyrozol, since long-term administration can result in further thyroid growth, which is associated with the risk of further constriction of the airways. Where necessary, treatment must be monitored particularly carefully. The treatment is preferably combined with thyroid hormones.

Preparation for Surgery in All Forms of Hyperthyroidism
Normal metabolic activity of the thyroid gland is attained, as described above. Surgery should be performed as soon as normal function is achieved. Otherwise, supplementary thyroid hormones must be administered. In the last 10 days before surgery, the surgeon may prefer to administer iodine to consolidate the thyroid tissue.

When preparing patients with hyperthyroidism for surgery, treatment with Thyrozol can be commenced about 3-4 weeks prior to the scheduled time of operation (or earlier in individual cases) and discontinued on the day before surgery.

Treatment Before Radioiodine Therapy
Normal metabolic activity of the thyroid gland is attained, as described above.

Thyrozol reduces the biological half-life of iodine in the thyroid tissue. Therefore, higher radioiodine doses may be necessary.

Dosage in Children
Initial dose depending on the severity of the disease: 0.3 - 0.5 mg/kg body weight per day.

Maintenance dose: 0.2 - 0.3 mg/kg body weight per day.

Additional treatment with thyroid hormone may be required.

Special Populations
In pregnant women as low dose as possible 2.5 - 10 mg per day should be selected and treatment be carried out without the additional administration of thyroid hormone.

In patient with liver damage the dose should be kept as low as possible.

Method of Administration
Take Thyrozol tablets whole with some liguid (e.g. ½ glass of water) after meals.

In initial therapy of hyperthyroidism, the above specified single doses should be taken at regular intervals

throughout the day. The maintenance dose can be taken all at once in the morning after breakfast.

3.3 Contraindications

Thyrozol must not be used in patients with:

- Hypersensitivity to Thiamazole, other thiourea derivatives or to any of the excipients listed in section 5.1 List of Excipients
- Moderate to severe blood count disturbances (granulocytopenia)
- Pre-existing cholestasis not caused by hyperthyroidism
- Previous damage to bone marrow after treatment with Thiamazole or Carbimazole.
- A history of acute pancreatitis after administration of Thiamazole or its prodrug Carbimazole

Combination therapy with Thiamazole and thyroid hormones is contraindicated during pregnancy (*see section 3.6 Fertility, Pregnancy, and Lactation*).

3.4 Special Warnings and Special Precautions for Use

Thyrozol should not be used in patients with:

- History of mild hypersensitivity reactions (e.g. allergic rashes, pruritus).

Thiamazole should only be used in short-term treatment and with careful monitoring in patients with

- Large goitres with constriction of the trachea because of the risk of goitre growth.

Vasculitis

In the event of the appearance of symptoms of vasculitis, the drug should be discontinued if necessary. In general, the symptoms are reversible after discontinuation of therapy.

Myelotoxicity

Agranulocytosis has been reported to occur in about 0.3 to 0.6% of cases. Therefore, patient must be informed prior to the start of therapy of the related symptoms (stomatitis, pharyngitis, fever). It usually occurs during the first weeks of treatment, but may still become manifest some months after the start of therapy and upon its reintroduction. Close monitoring of blood count is recommended before and after initiation of therapy especially in cases with pre-existing mild granulocytopenia. In the case that any of these symptoms are observed, especially during the first weeks of treatment, patients should be advised to contact their physician immediately for a blood count. If agranulocytosis is confirmed, a discontinuation of the medicinal product is necessary.

Other myelotoxic adverse reactions rarely occur in the recommended dose range. They have frequently been reported in connection with very high doses of Thiamazole (about 120 mg per day). These dosages should be reserved for special indications (severe courses of disease, thyrotoxic crisis). Occurrence of damage to the bone marrow during treatment with Thiamazole requires discontinuation of the medication and, if necessary, switching to an anti-thyroid drug of another substance group.

Acute pancreatitis

There have been post-marketing reports of acute pancreatitis in patients receiving Thiamazole or its prodrug Carbimazole. In case of acute pancreatitis, Thiamazole should be discontinued immediately. Thiamazole must not be given to patients with a history of acute pancreatitis after administration of Thiamazole or its prodrug Carbimazole. Re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset.

Women of childbearing potential and pregnancy

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

The use of Thiamazole in pregnant women must be based on the individual benefit/risk assessment. If Thiamazole 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 3.6 Fertility, Pregnancy, and Lactation*).

Control of hyperthyroidism
Excess dosage can lead to subclinical or clinical hypothyroidism and goitre growth due to TSH increase. Therefore, the dose of Thiamazole should be reduced as soon as a euthyroid metabolic condition is achieved and, if necessary, Levothyroxine should be given additionally. It is not useful to discontinue Thiamazole altogether and to continue with Levothyroxine only.

Goitre growth under therapy with Thiamazole in spite of suppressed TSH is a result of the underlying disease and cannot be prevented by additional treatment with Levothyroxine.

Achievement of normal TSH levels is crucial to minimise the risk of occurrence or deterioration of endocrine orbitopathy. However, this condition is frequently independent of the course taken by the thyroid disease. Such a complication itself does not constitute a reason to change the adequate treatment regimen and is not to be regarded as an adverse reaction of appropriately performed therapy.

At a low percentage, late hypothyroidism can occur after anti-thyroid therapy without any additional ablative measures. This is probably not an adverse drug reaction, but to be regarded as inflammatory and destructive processes in the thyroid parenchyma due to the underlying disease.

The reduction in the pathologically increased energy consumption in hyperthyroidism can lead to a (generally desired) gain in body weight during treatment with Thiamazole. The patients are to be informed that their energy consumption normalises along with the improving clinical picture.

Excipients
Thyrozol contains lactose; therefore, patients with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

3.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Iodine deficiency increases, excess iodine reduces the response of the thyroid gland to Thyrozol. No further direct interactions with other medication are known. It should, however, be noted that in the presence of hyperthyroidism the break-down and excretion of other medication can be accelerated. With increasing normalisation of the thyroid function these also return to normal. If necessary, the doctor will have to correct the dosage. The activity of anticoagulants may be potentiated by anti-vitamin-K activity attributed to Thimazole.

3.6 Fertility, Pregnancy, and Lactation
Women of childbearing potential
Women of childbearing potential have to use effective contraceptive measures during treatment (*see section 3.4 Special Warnings and Special Precautions for Use*).

Pregnancy
Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.

Thiamazole is able to cross the human placenta.

Based on human experience from epidemiological studies and spontaneous reporting, Thiamazole 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.

Thiamazole 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 Thiamazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended (*see section 3.4 Special Warnings and Special Precautions for Use*).

Lactation
Thiamazole passes into breast milk where it can reach concentrations corresponding to maternal serum levels, so that there is a risk of hypothyroidism developing in the infant.

Breast-feeding is possible during Thiamazole treatment; however, only low doses up to 10 mg daily may be used without additional administration of thyroid hormones.

The infant's thyroid function is to be monitored regularly.

3.7 Effects on Ability to Drive and Use Machines
Thiamazole has no influence on the ability to drive and use machines.

3.8 Undesirable Effects
The assessment of undesirable effects is based on the following definitions of frequencies:

very common	≥ 1/10
common	≥ 1/100 to < 1/10
uncommon	≥ 1/1,000 to < 1/100
rare	≥ 1/10,000 to < 1/1,000
very rare	< 1/10,000

not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Uncommon
Agranulocytosis occurs in about 0.3 to 0.6% of cases. It may still become manifest weeks or months after the start of therapy and necessitates discontinuation of the medicinal product. Most cases recede spontaneously.

Very rare
Thrombocytopenia. Pancytopenia. Generalised lymphadenopathy.

Not known
Sialadenopathy.

Endocrine disorders
Very rare
Insulin autoimmune syndrome (with pronounced decline in blood glucose level).

Not known
Hypothyroidism.

Nervous system disorders
Rare
Disturbances in the sense of taste (dysgeusia, ageusia) occur rarely; they can recede after discontinuation of therapy. A return to normal can take several weeks, however.

Very rare
Neuritis. Polyneuropathia.

Not known
Paresthesia. Headache. Vertigo.

Vascular disorders
Not known
Vasculitis.

Gastrointestinal disorders
Very rare
Acute salivary gland swelling.

Not known
Nausea. Vomiting. Epigastric distress. Acute pancreatitis.

Hepatobiliary disorders
Very rare
Individual cases of cholestatic jaundice or toxic hepatitis have been described. The symptoms generally recede after discontinuation of the medicinal product. Clinically inconspicuous signs of cholestasis during treatment have to be differentiated from disturbances caused by hyperthyroidism, such as an increase in GGT (Gamma Glutamyl Transferase) and alkaline phosphatase or its bone specific isoenzyme.

Skin and subcutaneous tissue disorders
Very common
Allergic skin reactions of varying degrees (pruritus, rash, urticaria). They mostly take a mild course and frequently recede during continued therapy.

Very rare
Severe forms of allergic skin reactions including generalised dermatitis. Alopecia and abnormal loss of hair. Drug-induced lupus erythematosus.

Not known
Skin pigmentation.

Musculoskeletal and connective tissue disorders
Common
Arthralgia may develop gradually and occur even after several months of therapy.

Not known
Myalgia.

General disorders and administration site conditions
Rare
Drug fever.

Not known
Edema.

Psychiatric disorders
Not known
Drowsiness.

Paediatric population
Frequency, type and severity of adverse reactions in children appear to be comparable with those in adults. 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).

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.

3.9 Overdose
Overdose leads to hypothyroidism with corresponding symptoms of a reduced metabolism and, through the feedback effect, to activation of the anterior pituitary lobe with subsequent goitre growth. This can be avoided by dose reduction as soon as a euthyroid metabolic condition is achieved and, if necessary, by additional administration of Levothyroxine (*see section 3.2 Posology and Method of Administration*).

Negative consequences of accidental ingestion of high doses of Thiamazole are not known.

4. PHARMACOLOGICAL PROPERTIES
4.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Anti-thyroid preparation.

ATC Code: H03BB02.

Thiamazole inhibits dose-dependently the incorporation of iodine into tyrosine and thereby the neosynthesis of thyroid hormones. This property permits symptomatic therapy of hyperthyroidism regardless of its cause. Whether Thiamazole furthermore affects the 'natural course' taken by the immunologically induced type of hyperthyroidism (Graves' disease), i.e. whether it suppresses the underlying immunopathogenetic process, can presently not be decided with certainty. The release of previously synthesised thyroid hormones from the thyroid is not affected. This explains why the length of the latency period until normalisation of the serum

concentrations of thyroxine and triiodothyronine, and thus to clinical improvement, differs in individual cases. Hyperthyroidism is also unaffected by the release of hormones after destruction of the thyroid cells, e.g. after radioiodine therapy or in thyroiditis.

4.2 Preclinical Safety Data

Preclinical safety studies are available to a limited extent only.

Single-dose toxicity data show that the acute toxicity of Thiamazole is low.

In repeated-dose studies, bone marrow depression was seen at dose levels, which were considerably higher than the therapeutic dose levels.

Mutagenicity studies did not reveal any evidence of mutagenic or clastogenic effects.

In a two-year chronic toxicity study in rats no relevant findings other than pharmacologically mediated effects on the thyroid were observed. In a two-year chronic toxicity study in mice a higher incidence of hepatomas, which did not reach the level of statistical significance, was seen when Thiamazole was administered at a concentration of 500 mg/L in drinking water. The relevance of the latter finding is questionable and Thiamazole is not classified as a carcinogenic substance according to the IARC (International Agency for Research of Cancer) or NTP (National Toxicology Program) criteria.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Tablet core

Silica colloidal anhydrous, Magnesium stearate, Hypromellose, Talc, Cellulose powered, Maize starch, Lactose monohydrate, Sodium starch glycolate

Coating

Dimeticone 100, Macrogol 400, Hypromellose, Titanium dioxide (E 171), Iron oxide (E 172)

5.2 Shelf-life

The expiry date is indicated on the packaging.

5.3 Storage

Store in a dry place, below 30°C.

5.4 Package Quantities and Registration Number

Thyrozol® 5 mg, Box, 10 blisters @ 10 film-coated tablets	Reg. No. DKI0063401417A2
Thyrozol® 10 mg, Box, 10 blisters @ 10 film-coated tablets	Reg. No. DKI0063401417B2

HARUS DENGAN RESEP DOKTER

Manufactured by
Merck Healthcare KGaA, Darmstadt, Germany

Primary packed by
P&G Health Austria GmbH & Co. OG, Spittal, Austria

Imported and secondary packed by

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