Thyrozol®

5mg film-coated tablets
10mg film-coated tablets
Active ingredient: Thiamazole (methimazole)

Composition
Medicinally active ingredients:
Each Thyrozol 5mg film-coated tablet contains 5 mg thiamazole.
Each Thyrozol 10mg film-coated tablet contains 10 mg thiamazole

Excipients: Lactose monohydrate (see Special warnings and precautions for use), corn starch, cellulose powder, talc, methylhydroxypropyl cellulose, magnesium stearate, poly(O-carboxymethyl) starch sodium salt, silicon dioxide, Macrogol 400, dimethicone 100, colourings E 171 and E 172.

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 radioiodine treatment.
- Intermittent treatment after radioiodine therapy.
- In exceptional cases, for long-term therapy of hyperthyroidism where definite therapeutic measures are not applicable due to the patient's general condition, due to personal reasons or because they are rejected, and where Thyrozol (at the lowest possible dose) is well tolerated.
- Prophylactic treatment in patients with a history of hyperthyroidism and autonomous adenomas in whom iodine exposure is indispensable (e.g. examination with iodine-containing contrast media)

Posology and method of administration
General dosage recommendations

Dosage in adults
Inhibition of thyroid hormone production can usually be achieved with daily doses of 25 to 40 mg thiamazole. For mild cases, an initial dose of 20 mg thiamazole daily may be considered. In severe cases of hyperthyroidism an initial dose of 40 mg thiamazole may be required

The dose is individually adjusted depending on the metabolic condition of the patient, as indicated by the development of the thyroid hormone status.

For maintenance therapy, one of the following treatment options is recommended:

a) Daily maintenance dose of 5-20 mg thiamazole in combination with levothyroxine, in order to avoid hypothyroidism

b) Monotherapy with daily doses of 2.5 and 10 mg thiamazole..

Iodine-induced hyperthyroidism may possibly require higher dosages.

Dosage in children:
The initial dose depending on the severity of the disease is 0.3 – 0.5 mg/kg body weight per day.
After normalization of the thyroid function, the dose is gradually reduced to a lower maintenance dose of 0.2 – 0.3 mg/kg body weight per day, which depends on the metabolic condition of the patient. Additional treatment with thyroid hormone may be required to avoid hypothyroidism.

Conservative treatment of hyperthyroidism:
In conservative treatment of hyperthyroidism, therapy 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. In cases where remission of the disease cannot be achieved and definite therapeutic measures do not apply or are rejected, thiamazole may be used as long-term anti-thyroid therapy in as low a dosage as possible without addition or in combination with a low dose of levothyroxine.
Patients with large goiters and constriction of the trachea should, if at all, only undergo short-term treatment with thiamazole since long-term administration can result in goitre growth. It may be necessary to monitor therapy particularly thoroughly (TSH level, tracheal lumen). The treatment is preferably combined with thyroid hormones.

Pre-operative therapy
Temporary pre-treatment, (for about 3 to 4 weeks or longer, if individually needed), may serve to achieve a euthyroid metabolic condition thus reducing surgery-related risks.
Surgery should be performed as soon as the patient is euthyroid, as otherwise, supplementary thyroid hormones must be administered. Treatment may be terminated the day before surgery.
The thiamazole-induced increased brittleness and bleeding tendency of thyroid tissues may be compensated by additional pre-operative administration of high-dose iodine during the ten days preceding surgery (Plummer's iodine therapy).

Treatment prior to radioiodine therapy:
Achievement of a euthyroid metabolism, before initiation of radioiodine therapy is important particularly in severe hyperthyroidism, as post-therapeutic thyrotoxic crisis has occurred in individual cases after such therapy without pre-treatment.

Note: Thiourea derivatives may reduce the radiosensitivity of the thyroid tissue. In scheduled radioiodine therapy of autonomous adenoma, activation of paranodular tissue by means of pre-treatment must be prevented.

Intermittent antithyroid therapy after treatment with radioiodine
The duration and dose of treatment must be defined individually depending on the severity of the clinical picture and the estimated period until radioiodine therapy starts to be effective (approximately 4-6 months)

Long-term antithyroid therapy in cases where remission of the disease cannot be achieved and definite therapeutic measures do not apply or are rejected:
Thiamazole in as low a dose as possible (2.5-10 mg per day) without additional or together with a small amount of thyroid hormone.

Prophylactic treatment in patients with a history of hyperthyroidism and autonomous adenomas in whom iodine exposure is indispensable
In general, daily doses of 10 to 20mg thiamazole and/or 1g perchlorate are administered for approx. 10 days (e.g. for renally excreted contrast media). The duration of treatment depends on the period of time for which the iodine-containing substance is retained in the body.

<u>Special populations</u>
In patients with hepatic impairment, the plasma clearance of thiamazole is reduced. Therefore, the dose should be kept as low as possible and patients should be closely monitored.

Due to the lack of pharmacokinetic data for thiamazole in patients with renal impairment, careful individual dose adjustment under close monitoring is recommended. The dose should be as low as possible.
Although no accumulation is expected in elderly patients, careful individual dose adjustment with close monitoring is recommended.

<u>Administration</u>
The tablets are to be swallowed whole with sufficient liquid after meals.

During high-dose initial therapy of hyperthyroidism, the above stated single doses can be subdivided and taken at regular intervals over the day.

The maintenance dose can be taken all at once in the morning during or after breakfast

Contraindications
Thyrozol should not be used in patients with

- hypersensitivity to thiamazole, other thionamide derivatives or any of the excipients
- moderate to severe blood count disturbances (granulocytopenia)
- preexisting cholestasis not caused by hyperthyroidism
- previous damage to bone marrow after treatment with carbimazole or thiamazole.
- 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 Pregnancy and Lactation).

Special warnings and precautions for use
Thyrozol should not be used in patients with history of mild hypersensitivity reactions (e.g. allergic rashes, pruritus).

Thyrozol should only be used in short-term treatment and with careful medical monitoring in patients with large goitres with constriction of the trachea because of the risk of goitre growth.

Myelotoxicity
Agranulocytosis has been reported to occur in about 0.3 to 0.6% of cases. Therefore, patients must be informed prior to the start of therapy of the related symptoms (stomatitis, pharyngitis, fever). It usually occurs during the first few weeks of treatment, but may still manifest some months after the start of therapy and upon its reintroduction. A 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 occur, especially during the first few weeks of treatment, patients should be advised to contact their physician immediately for a blood count. If agranulocytosis is confirmed, the medicinal product must be discontinued.

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.

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.

Vasculitis
Cases of vasculitis have been observed very rarely in patients receiving thiamazole therapy. The cases of vasculitis include: leukocytoclastic cutaneous vasculitis, glomerulonephritis, and systemic vasculitis (with fatal outcome). Many cases were associated with anti-neutrophilic cytoplasmic antibodies (ANCA)-positive vasculitis. Early recognition of vasculitis is important to prevent long term organ damage and/or death. Inform patients to promptly report symptoms that may be associated with vasculitis including rash, hematuria or decreased urine output, dyspnea or hemoptysis. If vasculitis is suspected, discontinue thiamazole therapy and initiate appropriate intervention.

Women of childbearing potential and pregnancy
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.

Control of hypothyroidism
Excess dosage can lead to subclinical or clinical hypothyroidism and goiter 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 minimize 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 normalizes along with the improving clinical picture.

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

Pregnancy and Lactation

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

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.

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 function of the thyroid gland of the neonate has to be monitored regularly.

Interactions with other medicinal products and other forms of interaction
Iodine deficiency increases the response of the thyroid to thiamazole, whereas iodine excess lowers the response. Further direct interactions with other medicinal products are not known. However, it should be taken into account that the metabolism and elimination of other medicinal products can be accelerated in hyperthyroidism. . They normalize in correlation with increasing normalization of the thyroid function. The dosage must be adjusted where necessary.

Furthermore, there are signs indicating that improvement of hyperthyroidism may normalize the enhanced activity of anticoagulants in hyperthyroid patients.

Effects on ability to drive and use machines
Thiamazole does not affect the ability to drive a vehicle or to operate machinery

Undesirable effects
The assessment of adverse reactions is based on the following frequency grouping:

Very common ≥ 1/10
Frequently ≥ 1/100, <1/10
Uncommon ≥ 1/1000, < 1/100
Rare ≥ 1/10000, < 1/1000
Very rare < 1/10000
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Uncommon
Agranulocytosis occur in about 0.3-0.6 % of cases. It can still manifest weeks or months after the start of therapy and necessitate discontinuation of the medication. In most cases, it recedes spontaneously.

Very rare
Thrombocytopenia, pancytopenia, generalized lymphadenopathy.

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

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.

Vascular disorders
Frequency 'not known'
Vasculitis

Gastrointestinal disorders
Very Rare
Acute salivary gland swelling
Frequency 'not known'
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 inapparent 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 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 generalized dermatitis. Alopecia. Drug-induced lupus erhtyematosus.

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

General disorders and administration site conditions
Rare
Drug fever.

Overdose
Overdose leads to hypothyroidism with the corresponding symptoms of reduced metabolism and, through the feedback effect, to activation of the anterior pituitary lobe with subsequent goiter 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 "Posology and method of administration")

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

Pharmacokinetics
Thiamazole is absorbed rapidly and completely. After administration, maximum serum levels are reached within 0.4 to 1.2 hours.
Protein binding is negligibly low. Thiamazole accumulates in the thyroid where it is metabolised only slowly. In spite of fluctuating serum levels, the accumulation of thiamazole in the thyroid gland still leads to a concentration plateau. This results in a duration of action of nearly 24 hours for the single dose. According to present knowledge, the kinetics of thiamazole is independent of thyroid function.
The elimination half-life is about 3 to 6 hours and is prolonged in hepatic insufficiency. Thiamazole undergoes renal and biliary elimination; excretion with the faeces is slight, suggesting enterohepatic circulation. 70% of the substance are excreted by the kidneys within 24 hours. Only a small amount is excreted in unchanged form. At present, no experience is available on the pharmacological activity of the metabolites.

Pharmacodynamics
Thiamazole inhibits dose-dependently the incorporation of iodine into tyrosine and thereby the neo-synthesis 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 immunopathogenitic 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 due to the release of hormones after destruction of thyroid cells, e.g. after radioiodine therapy or in thyroiditis, is also not affected.

Storage
Store below 30°C.

Presentations
Thyrozol 5 mg: 100 tablets/box
Thyrozol 10 mg: 100 tablets/box
Not all presentations may be available locally

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Date of revision
July 2020