Thiamazole
Core Safety Profile

4.2 Posology and method of administration

Relevant safety information of section 4.2 included:

Special populations

In patients with hepatic impairment, the plasma clearance of thiamazole is reduced. Therefore, the dose should be kept as low as possible.

4.3 Contraindications

Thyrozol must not be used in patients with

- Hypersensitivity to thiamazole**,** other thionamide derivatives or to any of the excipients (see section 6.1),
- Moderate to severe blood count disturbances (granulocytopenia),
- Pre-existing cholestatic disease not caused by hyperthyroidism,
- Previous damage to bone marrow after treatment with thiamazole or carbimazole.

Combination therapy with thiamazole and thyroid hormones is contraindicated during pregnancy (see section 4.6).

4.4 Special warnings and 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 under careful monitoring in patients with

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

Agranulocytosis has been reported to occur in about 0.3 to 0.6% of cases and the patient´s attention should be drawn to its symptoms (stomatitis, pharyngitis, fever) prior to the start of therapy. 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. 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 are observed, especially during the first weeks of treatment, patients should be advised to contact their physician immediately for a blood count. If an agranulocytosis is confirmed, a discontinuation of the medicinal product is necessary.

Other myelotoxic adverse reactions are rare with the recommended doses. 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 forms of disease, thyrotoxic crisis). Occurrence of bone marrow toxicity during treatment with thiamazole requires discontinuation of the medicinal product and, if necessary, switch to an anti-thyroid medicinal product of another substance group.

Excess dosage can lead to sub-clinical 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 is no reason to change the adequate treatment regimen and is not to be regarded as an adverse reaction to the correctly carried out therapy.

At a low percentage late hypothyroidism may occur after anti-thyroid therapy without any additional ablative measures. This is probably not an adverse reaction to the medicinal product, but to be regarded as inflammatory and destructive processes in the parenchyma of the thyroid 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. Patients should be informed that improvement of the clinical picture indicates normalisation of their energy consumption.

Thyrozol contains lactose; therefore its use is not recommended in patients with rare hereditary disorders of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction 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 normalise in correlation with increasing normalisation of thyroid function. The dosage must be adjusted where necessary.

Furthermore, there is evidence that correction of hyperthyroidism may normalise the enhanced activity of anticoagulants in hyperthyroid patients.

4.6 Pregnancy and lactation

Untreated hyperthyroidism during pregnancy may lead to serious complications such as premature birth and malformation. However, hypothyroidism caused by treatment with inappropriate thiamazole doses is also associated with a tendency to abortion.

Thiamazole passes the placental barrier and, in foetal blood, reaches concentrations equal to those found in maternal serum. At an inappropriate dosage, this may lead to goitre formation and hypothyroidism in the foetus as well as to reduced birth weight. There have been repeated reports of partial aplasia cutis on the head of neonates born to women treated with thiamazole. This defect healed spontaneously within a few weeks.

In addition, a certain pattern of diverse malformations has been associated with high-dose thiamazole therapy during the first weeks of pregnancy, e.g. choanalatresia, oesophageal atresia, hypoplastic nipples, delayed mental as well as motor development. In contrast, several case studies on prenatal thiamazole exposition have neither revealed any morphological development disorders nor affection of the thyroid or the physical and intellectual development of the children.

Since embryotoxic effects cannot be completely excluded, Thyrozol must only be administered during pregnancy after strict benefit risk evaluation and only at the lowest still effective dose level without additional administration of thyroid hormones.

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.

4.7 Effects on ability to drive and use machines

Thiamazole has no influence on the ability to drive and use machines.

4.8 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

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.

Endocrine disorders

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.

Gastrointestinal disorders

Very rare
Acute salivary gland swelling.

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. Drug-induced lupus erythematosus.

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.

4.9 Overdose

Overdose leads to hypothyroidism with corresponding symptoms of a reduced metabolism and, through the feedback effect, to activation of the adenohypophysis 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 4.2).

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