VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

The most common forms of hyperthyroidism include Graves' disease, Plummer disease, and toxic adenoma; but approximately 1-2% of patients with hyperthyroidism progress to thyroid storm, a rare disorder. (3) (4) (5)

The overall incidence of hyperthyroidism (condition in which the thyroid gland is overactive and makes excessive amounts of thyroid hormone) is estimated between 0.05% and 1.3%, with the majority consisting of subclinical disease. A population-based study in the United Kingdom and Ireland found an incidence of 0.9 cases per 100,000 children younger than 15 years, showing that the disease incidence increases with age. The incidences of Graves' disease and Plummer disease change with iodine intake. The prevalence of hyperthyroidism is approximately 5-10 times less than hypothyroidism (condition in which the body lacks sufficient thyroid hormone). (4) (5)

Autoimmune thyroid disease (when the immune system creates antibodies that cause the thyroid to grow and make more thyroid hormone than the body needs) occurs with the same frequency in Caucasians, Hispanics, and Asians but at lower rates in African Americans; but all thyroid diseases occur more frequently in women than in men. (4) (5)

VI.2.2 Summary of treatment benefits

Thiamazole was introduced into use in 1954 and is still widely used for the temporary relief of hyperthyroidism in Graves' disease, particularly in patients with mild or self-limited hyperthyroidism or who wish to avoid removal of the thyroid gland (thyroidectomy) or radiation therapy. (6)

Generally, there are two antithyroid medications available (propylthiouracil and thiamazole) for hyperthyroidism. Thiamazole works, as does propylthiouracil, to reduce the levels of thyroid hormone by decreasing thyroid hormone production. (7) (8)

The main benefit of thiamazole compared to propylthiouracil is that it can be taken one, two, or three times a day (depending on your dosage), which may have some advantage in terms of drug compliance. This issue has been carefully studied, with increased compliance noted in the groups of patients treated with once a day thiamazole dosing. (7)

Furthermore, thiamazole is usually preferred over propylthiouracil because it reverses hyperthyroidism more quickly and has fewer side effects. Because of the hepatotoxicity of propylthiouracil which can lead to death, thiamazole is now considered the first line treatment for hyperthyroidism when there is a need to avoid surgery or radioiodine therapy. (6) (8) (9)

VI.2.3 Unknowns relating to treatments benefits

Some missing information was identified regarding thiamazole use: firstly, the safety and efficacy of thiamazole in children under 2 years old has not been systematically studied; secondly, there is a lack of data regarding pharmacokinetic behaviour of thiamazole in patients with renal impairment. For the reasons outlined above, thiamazole is not recommended in children under 2 years old and careful individual dose adjustment under close monitoring is recommended in patients with renal impairment.

VI.2.4 Summary of safety concerns

Important identified risk

Risk	What is known	Preventability
Myelotoxic (decrease in production of cells) adverse reactions	Some severe adverse effects related to myelopoiesis (the process of making new white blood cells) have been reported with thiamazole: agranulocytosis (lowered white blood cell count), granulocytopenia (marked decrease in the granulocytes number), thrombocytopenia (low blood platelet count), and aplastic anaemia (condition that occurs when the body stops producing enough new blood cells). (10) Agranulocytosis is a potentially life-threatening adverse effect	The patient´s attention should be drawn to agranulocytosis's symptoms prior to the start of therapy. (10) A close monitoring of blood count is recommended before and after initiation of therapy especially in cases with pre-existing mild granulocytopenia. (1) (2) (10) Furthermore, thiamazole should be used with extreme caution in patients receiving other drugs known to cause agranulocytosis. (10)

Risk	What is known	Preventability
	of thiamazole therapy. Most cases of agranulocytosis appear to occur within the first 2 months of therapy, but rarely may occur after 4 months of therapy. (2) (10) The most common symptoms are stomatitis (inflammation of the mouth and lips), pharyngitis (a sore throat caused by inflammation of the back of the throat), fever. If an agranulocytosis is confirmed, a discontinuation of the medicinal product is necessary. (1) (2) (10) Although thiamazole-induced granulocytosis may be dose related (possibly occurring more frequently with higher dosages of the drug), agranulocytosis may occur irrespective of dosage, length of treatment, or previous exposure to the antithyroid drug, and may occur more frequently in geriatric patients. (10) Occurrence of bone marrow toxicity during treatment with thiamazole requires discontinuation of the medicinal product. (1) (2) (10)	
Goitre growth	Excess dosage can lead to sub-clinical or clinical goitre growth	Monitoring of serum thyroxine is necessary. (2)

Risk	What is known	Preventability
	(growth of the thyroid gland). (2) Goitre growth has been reported commonly with use of thiamazole. (2)	Thiamazole should only be used in short-term treatment and under careful monitoring in patients with large goitres with constriction of the trachea. (2) 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. (2)
Use during pregnancy	Thiamazole readily crosses the placental membranes and may cause foetal harm, particularly when administered in the first trimester of pregnancy. The drug can also cause foetal goiter and hypothyroidism (cretinism), as well as reduced birth weight, when administered to a pregnant woman. (2) (10) 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. (2) In addition, a certain pattern of	Thiamazole should be used with caution in pregnant and breastfeeding women. (2) Since embryotoxic effects cannot be completely excluded, thiamazole 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. (2)

Risk	What is known	Preventability
	diverse malformations has been associated with high-dose thiamazole therapy during the first weeks of pregnancy, e.g. choanalatresia (congenital disorder where the back of the nasal passage is blocked), oesophageal atresia (obstruction of the esophagus), hypoplastic (underdeveloped) 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. (2) (11) These specific birth defects were associated with the use of thiamazole during the first trimester of pregnancy but were not found when the drug was administered later in pregnancy. (10)	
Use during breastfeeding	Thiamazole crosses the placenta and passes into breast milk. (2) 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	Thiamazole should be used with caution in breastfeeding women. (2) Breast-feeding is possible during thiamazole treatment; however, only low doses up to 10 mg daily may be used without additional administration of thyroid

Risk	What is known	Preventability
	the infant. (1) (2) Nevertheless, thiamazole generally is compatible with breast-feeding, and moderatedosages of the drug appear to be safe during breastfeeding. (1) (10)	hormones. (2) The function of the thyroid gland of the neonate has to be monitored regularly. (2) (10)
Use in patients with history of mild hypersensitivity reactions	Cross-sensitivity between thiomides may occur (i.e., in approximately 50% of patients switched from one thioamide agent to the other). (10) Some skin and subcutaneous tissue disorders have been reported with thiamazole: allergic skin reactions of varying degrees (pruritus, rash, urticaria), systemic lupus erythematosus-like reaction and severe forms of allergic skin reactions including generalised dermatitis, alopecia, drug-induced lupus erythematosus. (2)	Thiamazole Uni-Pharma must not be used in patients with hypersensitivity to thiamazole, other thionamide derivatives or to any ingredient in this formulation. (2) Furthermore, thiamazole should not be used in patients with history of mild hypersensitivity reactions (e.g. allergic rashes, pruritus). (2) In patients experiencing serious allergic reactions to thiamazole, some clinicians state that using the alternative antithyroid drug is not recommended. (10)
Use in patients with metabolic disorders	Thiamazole Uni-Pharma contains lactose. (2) Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, present a deficiency in lactase production (enzyme) causing gastrointestinal symptoms. (12)	Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. (2)

Important potential risk

Risk	What is known (including reason why it is considered a potential risk)
Overdose	In general, overdosage of thiamazole may be expected to produce effects that are extensions of common adverse reactions. Symptoms may include nausea, vomiting, epigastric distress (pain or discomfort in the upper part of the abdomen), headache, fever, joint pain, pruritus, and oedema. Aplastic anaemia (pancytopenia) or agranulocytosis may be manifested in hours to days. Agranulocytosis is the most serious effect associated with thiamazole overdosage. Less frequent adverse effects include exfoliative dermatitis, hepatitis, nephrotic syndrome, neuropathies, and central nervous system stimulation or depression. Overdose may also lead to hypothyroidism with corresponding symptoms of a reduced metabolism and, through the feedback effect, to activation of the adenohypophysis (part of the pituitary gland that regulates hormone production) 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). (1) (2) (10) (13) No data are available on the median lethal dose of thiamazole or the concentration of drug in biologic fluids associated with toxicity and/or death. (10) (13) Treatment of thiamazole overdosage generally involves appropriate supportive care as dictated by the patient's medical status. Clinicians should consider consulting a poison control centre for the most current information on the management of thiamazole overdosage. (10) (13) Generally, gastric emptying, charcoal and monitoring are made. Control of bone marrow and hepatic function should also be made. (2)
Hypothyroidism (low thyroid hormone level)	Thiamazole may cause hypothyroidism and goitre growth, necessitating routine monitoring of thyrotropin (thyroid stimulating hormone) and free thyroxine concentrations. Therefore, dosage should be reduced as soon as a euthyroid metabolic condition (the state of having normal thyroid gland function) is achieved and, if necessary, levothyroxine should be

	given additionally. Nevertheless, it is not useful to discontinue thiamazole altogether and to continue with levothyroxine only. (2) (10) 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 (the basic cellular tissue comprising the thyroid gland) due to the underlying disease. (2)
Use in patients with hepatic impairment	Thiamazole should be used with caution in patients with hepatic disorder, since plasma clearance of thiamazole is reduced in these patients (half-life may be prolonged in the presence of hepatic impairment). Therefore, the dose should be kept as low as possible and patients should be closely monitored. (1) (2) Patients with symptoms suggestive of hepatic dysfunction (e.g., anorexia, pruritus, right upper-quadrant pain) should have prompt evaluation of their liver function (alkaline phosphatase, bilirubin) and hepatocellular integrity (ALT, AST). (10) (13) Thiamazole Uni-Pharma must not be used in patients with pre-existing cholestasis (a condition where bile cannot flow from the liver to the duodenum) not caused by hyperthyroidism. (2)
Hepatic disorders	Although there have been reports of hepatotoxicity (including acute liver failure) associated with thiamazole, the risk of hepatotoxicity appears to be low. Jaundice associated with thiamazole-induced hepatitis may persist for several weeks after discontinuance of the drug. (1) (2) (10) (13) Therefore, patients should be informed of the adverse hepatic effects associated with thiamazole and advised to immediately discontinue the drug and promptly contact their clinician if pruritic rash, jaundice, acholic (with absence of bile) stools, dark urine, arthralgias, abdominal pain, nausea, or fatigue occurs. If there is evidence of a clinically important liver abnormality, including hepatic aminotransferase concentrations exceeding 3 times the upper limit of normal, the drug should be discontinued promptly. (10) (13)
Increased body weight	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. (2)

Missing information

Risk	What is known
Use in patients with renal impairment	As there is a lack of data regarding pharmacokinetic behaviour of thiamazole in patients with renal impairment, careful individual dose adjustment under close monitoring is recommended. The dose should be kept as low as possible. (2)
Use in children up to 2 years old	The safety and efficacy of thiamazole in children under 2 years old has not been systematically studied. Thiamazole is therefore not recommended in children under two years old. (2)

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6. Planned post authorisation development plan (if applicable)

This section is not applicable.

VI.2.7. Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
0001	19/02/2016	Not applicable.	First version of the RMP
0002	04/05/2016	Not applicable.	Update of PIL to include Iceland as CMS

	EU-RISK MANAGEMENT PLAN
UNI-PHARMA	THIAMAZOLE UNI-PHARMA 5 MG TABLETS

Version	Date	Safety Concerns	Comment
0003		Update on sections VI.2.1, VI.2.2, VI.2.3, VI.2.4 and VI.2.5.	Minor amendments were requested to the applicant following the "Reference Member State Day 70 Preliminary Assessment Report".