Direct Healthcare Professional Communication

for

Thiamazole / Thyrozol®

Subject:	**Medicinal products containing carbimazole or thiamazole (synonym: methimazole): (1) risk of acute pancreatitis and (2) update on risks during pregnancy**
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Dear Healthcare professional,

Merck Biopharma / EMD Serono in agreement with the European Medicines Agency (EMA) and the National Competent Authority would like to inform you on the following:

Summary

(1) Risk of acute pancreatitis

- Acute pancreatitis has been reported following treatment with carbimazole/thiamazole.
- If acute pancreatitis occurs, treatment with carbimazole/ thiamazole should be discontinued immediately.
- As re-exposure may result in recurrence of acute pancreatitis, with decreased time to onset, these medicines must not be given to patients with a history of acute pancreatitis following administration of carbimazole/thiamazole.

(2) Update on risks during pregnancy

- Carbimazole and its active metabolite thiamazole are suspected to cause congenital malformations when administered during pregnancy, particularly when administered in the first trimester of pregnancy and at high doses.
- Women of childbearing potential have to use effective contraceptive measures during treatment with carbimazole/thiamazole.
- Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.
- Carbimazole/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 carbimazole/thiamazole is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.

Background on the safety concern

General information

Medicinal products containing carbimazole or thiamazole are used in the management of Treatment of hyperthyroidism, including:

- Conservative treatment of hyperthyroidism, especially in small or absent goiter,
- Preparation for surgery in all forms of hyperthyroidism,
- Preparation for radioiodine treatment particularly in patients with severe hyperthyroidism,
- Intermediate therapy after treatment with radioiodine,
- Prophylactic treatment in patients with sub-clinical hyperthyroidism, autonomous adenomas or a history of hyperthyroidism, in whom exposure to iodine is indispensable (e.g. examination with iodine-containing contrast media).

Risk of acute pancreatitis

There have been post-marketing reports of acute pancreatitis with the use of medicinal products containing carbimazole or thiamazole, including several cases in which a causal association was demonstrated.

While the mechanism is poorly understood, the presence of cases reporting recurrent acute pancreatitis with a decreased time to onset after re-exposure to carbimazole/thiamazole might suggest an immunological mechanism.

Immediate discontinuation of medicinal products containing carbimazole / thiamazole is required in patients who develop acute pancreatitis following exposure to carbimazole or thiamazole. Carbimazole/thiamazole must not be restarted and affected patients should be switched to an alternative therapy on the basis of the individual benefit/risk assessment.

Any future re-exposure to carbimazole/thiamazole in patients who have experienced acute pancreatitis with carbimazole or thiamazole in the past must be avoided, since it may result in recurrence of potentially life-threatening acute pancreatitis, with decreased time to onset.

The product information for medicinal products containing carbimazole/thiamazole will be updated accordingly, including the addition of a new contraindication of use in patients with a history of acute pancreatitis after administration of carbimazole or thiamazole.

Update on risks during pregnancy

Even though the epidemiological evidence remains controversial, an increased risk for congenital anomalies was shown in retrospective cohort studies which are characterized by the largest groups exposed to carbimazole/thiamazole in the first trimester of pregnancy to date.

The contribution of maternal hyperthyroidism to the risk of congenital anomalies is poorly understood.

There is some evidence from epidemiological studies that a higher dose of carbimazole/thiamazole might be associated with a higher risk of congenital anomalies as compared with a lower dose.

All meta-analyses available to date showed an increased risk for congenital anomalies in association with the use of carbimazole/thiamazole during pregnancy.

The results of two larger retrospective cohort studies also suggest that a switch between different antithyroid agents during the first trimester of pregnancy is not beneficial about the incidence of major congenital malformations.

The mechanism underlying carbimazole/thiamazole embryopathy remains unknown.

The analysis of cases from spontaneous reporting revealed a certain pattern of congenital anomalies in association with the use of carbimazole/thiamazole during pregnancy.

Aplasia cutis congenita and craniofacial malformations (choanal atresia; facial dysmorphism) were the most frequently reported congenital malformations. In addition, there have been repeated reports of other congenital malformations including exomphalos, esophageal atresia, omphalo-mesenteric duct anomaly, and ventricular septal defect.

The vast majority of congenital anomalies reported with carbimazole/thiamazole was associated with the use of carbimazole/thiamazole in the first trimester of pregnancy.

Taking into account all available evidence to date, it is recommended that women of childbearing potential use effective contraceptive measures during treatment with carbimazole/thiamazole.

The use of carbimazole/thiamazole during pregnancy should be preserved for the situations in which a definite therapy of the underlying disease (thyroidectomy or radioiodine treatment) was not suitable prior to pregnancy and in case of new occurrence/reoccurrence during pregnancy as well as in case of an unplanned pregnancy.

Carbimazole/thiamazole must only be administered during pregnancy after a strict individual benefit/risk assessment and only at the lowest still effective dose level without additional

administration of thyroid hormones, taking into account the risks of maternal disease and the suspected teratogenic potential of carbimazole/thiamazole.

When carbimazole is given during pregnancy, close maternal, fetal and neonatal surveillance is recommended.

The product information for medicinal products containing carbimazole or its active metabolite thiamazole will be updated accordingly, including the addition of the recommendation to use effective contraceptive measures during treatment.

Call for reporting

Company contact point

If you require further medical information on thiamazole/Thyrozol® or would like to have a paper copy of the SmPC, please to contact Representative Office of Acino Pharma AG in Armenia