11th of January 2019

Medicinal products containing carbimazole or thiamazole (synonym: methimazole): (1) risk of acute pancreatitis and (2) strengthened advice on contraception

Dear Healthcare professional,

Remedica Ltd in agreement with the European Medicines Agency and the Medicines Authority of Malta would like to inform you of 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) Strengthened advice on contraception

- New review of available evidence from epidemiological studies and case reports strengthens the evidence that carbimazole/ thiamazole is suspected to cause congenital malformations when administered during pregnancy, particularly 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 all conditions where reduction of thyroid function is required including hyperthyroidism, preparation for thyroidectomy in hyperthyroidism and therapy prior to and post radio-iodine treatment.

Carbimazole is a prodrug which undergoes rapid metabolism to the active metabolite, thiamazole. Thiamazole is an antithyroid agent that acts by blocking the production of thyroid hormones.

Risk of acute pancreatitis

There have been post-marketing reports of acute pancreatitis with the use of medicinal products containing carbimazole/thiamazole.

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 based on 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.

Strengthened advice on contraception

A new review of available evidence from epidemiological studies and case reports strengthens the evidence that carbimazole/thiamazole can be associated with an increased risk of congenital malformations, especially when administrated in the first trimester of pregnancy and at high doses.

Reported malformations include aplasia cutis congenita (absence of a portion of skin (often localised on the head)), craniofacial malformations (choanal atresia; facial dysmorphism), defects of the abdominal wall and gastrointestinal tract

(exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly), and ventricular septal defect.

Recommendations

It is therefore 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 definitive therapy of the underlying disease (thyroidectomy or radioiodine treatment) was not suitable prior to pregnancy and in case of new occurrence or reoccurrence during pregnancy.

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.

The product information for medicinal products containing carbimazole/thiamazole will be updated accordingly.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with medicinal products containing carbimazole or thiamazole (synonym: methimazole) in accordance with the national spontaneous reporting system. Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt.

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Yours faithfully,

Andreas Vasiliou

Head of Drug Safety Department/QPPV

Remedica Ltd