25 February 2019

Dear Healthcare Professional

Carbimazole: (1) risk of acute pancreatitis and (2) advice on the importance of contraception

Amdipharm Mercury (Australia) Pty Ltd (an Advanz Pharma company), in agreement with the Therapeutic Goods Administration, would like to inform you of the following:

Summary

(1) Risk of acute pancreatitis

- Acute pancreatitis has been reported following treatment with carbimazole.
- If acute pancreatitis occurs, treatment with carbimazole 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 that occurred following administration of carbimazole.

(2) Advice on the importance of contraception

- Review of new available evidence from epidemiological studies and case reports strengthens the evidence that carbimazole 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 must use effective contraceptive measures during treatment with carbimazole.
- Hyperthyroidism in pregnant women should be adequately treated to prevent serious maternal and foetal complications.
- Carbimazole 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 is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.

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Background on the safety concern

General information

Medicinal products containing carbimazole are used in the management of 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 in its own right that acts by blocking the production of thyroid hormones.

Whilst the same safety concerns equally apply to Thiamazole, it has not been further considered in this communication as it is not registered in Australia.

Risk of acute pancreatitis

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

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 might suggest an immunological mechanism.

Immediate discontinuation of medicinal products containing carbimazole is required in patients who develop acute pancreatitis following exposure to carbimazole. Carbimazole 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 in patients who have experienced acute pancreatitis with carbimazole 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 will be updated accordingly.

Advice on the importance of contraception

A new review of available evidence from epidemiological studies and case reports strengthens the evidence that carbimazole is 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.

<u>Recommendations</u>

It is therefore recommended that women of childbearing potential use effective contraceptive measures during treatment with carbimazole.

The use of carbimazole during pregnancy should be reserved for situations in which a definitive therapy of the underlying disease (thyroidectomy or radioiodine treatment) was not suitable prior to pregnancy and where use of alternative therapy is not appropriate.

Carbimazole 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 is used during pregnancy, close maternal, foetal and neonatal monitoring is recommended.

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

ADVANZ PHARMA

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the Therapeutic Goods Administration.

Report ADRs online via https://www.tga.gov.au/reporting-adverse-events

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼
- unexpected adverse events

For more information please visit the TGA website https://www.tga.gov.au/reporting-adverse-events

You can also report adverse events to the sponsor for Neo-Mercazole:

Company name	E-mail	Telephone number	Fax Number
Amdipharm Mercury (Australia) Pty Ltd	medinfo.au@advanzpharma.com	1800 627 680	02 9928 7809

Your's sincerely

Anju Agarwal.

Dr. Anju Agarwal

Head of Drug Safety

Amdipharm Mercury (Australia) Pty Ltd