Jan-2019

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

Dear Healthcare professional,

Amdipharm UK Limited, Morningside Healthcare Limited, Essential-Healthcare Limited, Flamingo Pharma UK Limited, Accord-UK Limited and Macleods Pharma UK Limited, in agreement with the European Medicines Agency and the MHRA, 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 that occurred 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.

***Thiamazole (synonym: methimazole) is not currently licensed in the UK.**

Background on the safety concern

General information

Medicinal products containing carbimazole or thiamazole 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 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 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.

Strengthened advice on contraception

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

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

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 ▼

It is easiest and quickest to report ADRs online via the Yellow Cards website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store.

Alternatively, prepaid Yellow Cards for reporting are available by writing to FREEPOST YELLOW CARD (no other address details necessary); by emailing yellowcard@mhra.gov.uk; at the back of the British National Formulary (BNF); by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789; or by downloading and printing a form from the Yellow Card website.

You can also report adverse events to the following marketing authorisation holders:

Company name	**E-mail**	**Telephone number**	**Fax Number**
Amdipharm UK Limited	medicalinformation@advanzpharma.com	+44 (0) 8700 70 30 33	+ 44 (0) 20 8588 9200
Morningside Healthcare Ltd	medicalenquiry@morningsidehealthcare.com	+44 (0) 1162045950	
Essential-Healthcare Ltd	pv@essential-healthcare.co.uk	+44(0)1277 286 199	+44 (0)1733 72 70 30
Flamingo Pharma UK Ltd	safety@flamingopharma.co.uk	+44(0)208 901 3370	44(0) 208 861 4867
Macleods Pharma UK Limited	eusafety@macleodspharma.com	+44 (0) 800 023 6165	-
Accord-UK Ltd	medinfo@accord-healthcare.com	+44 (0) 1271 385257	+44 (0) 1271 346106

Company contact point

Company name	**Name of contact person**	**Contact Details**
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		+44 116 204 5951
Essential-Healthcare Ltd	Niket Shah (Director)	**E-mail:** niket.shah@essential-healthcare.co.uk **Telephone number:** +44 1277 286 199
Flamingo Pharma UK Ltd.	Sarika Pardhe General Manager Dr. Naveen Chamalli Shivakumar EU -QPPV	**E-mail:** sarika.pardhe@flamingopharma.com **Telephone number:** +91 022 33107576 +91 9881145403 E-mail: naveencs@lambda-cro.com Telephone Number: Mobile (24 X 7 day): +44 (0)7507477573 Tel: + 44(0) 208 901 3372
Macleods Pharma UK Limited	Dr. Ashish Mungantiwar Head – Pharmacovigilance Dr. Naveen Chamalli Shivakumar EU -QPPV	**E-mail:** drashish@macleodspharma.com eusafety@macleodspharma.com **Telephone Number:** +91-9867023914 **E-mail:** naveencs@lambda-cro.com **Telephone Number:** Mobile (24 X 7 day): +44 (0)7507477573 Tel: + 44(0) 208 901 3372
Accord-UK Ltd	Lisa Hughes Deputy QPPV, PV Operations	**E-mail**: PLRP-UK@accord-healthcare.com **Telephone Number**: +44 (0) 1271 385487

On behalf of all MAHs,

Signed by:

Anju Agarwal 11-Jan-2019

Dr. Anju Agarwal

Head of Drug Safety

Amdipharm UK Limited