

# Drug Safety Update



# MHRA

## Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 12 Issue 7 February 2019

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The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.



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First, read two updates on carbimazole, authorised for hyperthyroidism. See page 2 for strengthened advice to avoid carbimazole in pregnancy following a review of evidence for the known increased risk of congenital malformations. See page 4 for new warnings about cases of acute pancreatitis associated with treatment with carbimazole, which requires immediate and permanent discontinuation.

On page 5, we advise you of reports of Fournier's gangrene associated with SGLT2 inhibitors. Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) is a rare but life-threatening infection that needs to be identified and treated urgently.

Finally, see letters and alerts sent to healthcare professionals on page 7, including a letter sent to prescribers and dispensers of Lartruvo ▼ (olaratumab), authorised for advanced soft tissue sarcoma, to announce that no new patients should be prescribed Lartruvo after clinical trial data suggesting no survival benefit in combination with doxorubicin compared with doxorubicin alone. While further assessment of the study results is ongoing, treatment with olaratumab may continue in patients who are experiencing clinical benefit.

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## **Carbimazole: increased risk of congenital malformations; strengthened advice on contraception**

Carbimazole is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses. Women of childbearing potential should use effective contraception during treatment with carbimazole.

### **Advice for healthcare professionals:**

- carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, particularly in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily)
- women of childbearing potential should use effective contraception during treatment with carbimazole
- carbimazole should only be considered in pregnancy after a thorough individual assessment of benefits and risks of treatment, and only at the lowest effective dose without additional administration of thyroid hormones; close maternal, foetal, and neonatal monitoring is recommended
- please report to the [Yellow Card Scheme](#) any suspected adverse reactions associated with medicines taken during pregnancy experienced by women or the baby or child

### **Background**

Carbimazole is authorised for use in the management of hyperthyroidism, including preparation for thyroidectomy and treatment before and after radioiodine treatment. Around 45,000–50,000 prescriptions for carbimazole a month are dispensed across GP practices in NHS England (data from [openprescribing.net](#)).

Carbimazole is a prodrug that undergoes rapid metabolism to the active metabolite, thiamazole. Thiamazole (synonym methimazole) is an antithyroid agent that acts by blocking the production of thyroid hormones. Thiamazole is not authorised for use in the UK.

### **Risk of congenital malformations**

Adequate treatment of hyperthyroidism in pregnant women prevents serious maternal and foetal complications.

[PRAC signal report, 26-29 November 2018 meeting.](#)

Carbimazole crosses the placental barrier and can cause foetal harm. An EU review of available evidence from epidemiological studies and case reports concluded there was evidence that carbimazole is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily).

[Letter to healthcare professionals.](#)

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.

### **New advice on contraception and pregnancy**

Women of childbearing potential should use effective contraception during treatment with carbimazole – see [FSRH statement on contraception for women using known teratogenic drugs or drugs with potential teratogenic effects](#). The Patient Information Leaflet advises patients to tell their doctor straight away if they think they may be pregnant or are planning to have a baby.

Carbimazole must only be used during pregnancy when clinically indicated and after a strict individual benefit/risk assessment and only at the lowest effective dose without additional administration of thyroid hormones. The use of carbimazole 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.

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

### **Report suspected adverse drug reactions via the Yellow Card scheme**

Please continue to report any suspected adverse drug reactions via the [Yellow Card Scheme](#). Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card.

For more about the importance of reporting suspected adverse drug reactions associated with medicines in pregnancy see [Drug Safety Update July 2018](#).

Healthcare professionals, patients, and caregivers can report suspected side effects via the [Yellow Card website](#) or via the Yellow Card App. Download the app today via [iTunes Yellow Card](#) for iOS devices or via [PlayStore Yellow Card](#) for Android devices.

You can also use the app to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. The App is also piloting [additional questions on medicine use during pregnancy](#) – download the app and try it out for yourself.

*Article citation: Drug Safety Update volume 12, issue 7: February 2019: 1.*

## Carbimazole: risk of acute pancreatitis

If acute pancreatitis occurs during treatment with carbimazole, immediately and permanently stop treatment. Re-exposure to carbimazole may result in life-threatening acute pancreatitis with a decreased time to onset.

### Advice for healthcare professionals:

- cases of acute pancreatitis have been reported very infrequently during treatment with carbimazole
- if acute pancreatitis occurs, stop carbimazole treatment immediately
- do not use carbimazole in patients with a history of acute pancreatitis in association with previous treatment
- re-exposure may result in life-threatening acute pancreatitis with a decreased time to onset
- report suspected adverse drug reactions to the [Yellow Card Scheme](#) immediately

### Background

Carbimazole is authorised for use in the management of hyperthyroidism, including preparation for thyroidectomy and treatment before and after radioiodine treatment. Around 45,000–50,000 prescriptions for carbimazole a month are dispensed across GP practices in NHS England (data from [openprescribing.net](#)). Carbimazole is a prodrug that undergoes rapid metabolism to the active metabolite, thiamazole. Thiamazole (synonym methimazole) is an antithyroid agent that acts by blocking the production of thyroid hormones. Thiamazole is not authorised for use in the UK.

### Risk of acute pancreatitis

An EU review has found post-marketing reports of acute pancreatitis associated with the use of products containing carbimazole and thiamazole. In the UK, no Yellow Card reports of acute pancreatitis associated with carbimazole treatment have been received over a period of 55 years; however, a small number of reports have been received in other countries. Although the mechanism for development of acute pancreatitis is poorly understood, the presence of cases reporting recurrent acute pancreatitis with a decreased time to onset after re-exposure to carbimazole suggests a possible immunological mechanism.

Carbimazole must be immediately discontinued in patients who develop acute pancreatitis during treatment. Patients should be switched to an alternative therapy on the basis of an assessment of the individual benefits and risks.

Re-exposure to carbimazole must be avoided in patients who have previously experienced acute pancreatitis with carbimazole or thiamazole as re-exposure may result in recurrence of potentially life-threatening acute pancreatitis, with a decreased time to onset. The product information for products containing carbimazole is being updated to include risk of acute pancreatitis.

*Article citation: Drug Safety Update volume 12, issue 7: February 2019: 2.*

[PRAC signal report, 26-29 November 2018 meeting](#)

[Letter to healthcare professionals](#)

## **SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum)**

If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and start treatment urgently (including antibiotics and surgical debridement). Fournier's gangrene is a rare but potentially life-threatening infection that requires urgent medical attention.

### **Advice for healthcare professionals:**

- post-marketing cases of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) have been associated with the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors
- Fournier's gangrene is a rare but serious and potentially life-threatening infection
- if Fournier's gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required)
- urogenital infection or perineal abscess may precede necrotising fasciitis
- advise patients to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise
- report suspected adverse drug reactions to a SGLT2 inhibitor to the [Yellow Card Scheme](#) without delay

### **Review of cases of Fournier's gangrene**

SGLT2 inhibitors are indicated for the treatment of type 2 diabetes. Medicines in the UK are those containing dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin ▼.

[PRAC signal report, 26-29 November 2018 meeting.](#)

An EU review has assessed reported cases of Fournier's gangrene across the class of SGLT2 inhibitors. Although diabetes mellitus is a risk factor for the development of Fournier's gangrene, some of the EU post-marketing reports were considered possibly to be related to the use of SGLT2 inhibitors. Fournier's gangrene usually occurs almost exclusively in men. However, around a third of the EU cases reviewed were reported in women. We are also aware of rare occurrences of Fournier's gangrene in patients on SGLT2 inhibitors in the USA (see [FDA safety announcement](#)).

[Letter to healthcare professionals.](#)

We have received 6 Yellow Card reports (four in men and two in women) of UK cases of Fournier's gangrene in association with SGLT2 inhibitors up to January 2019. This corresponds to a UK estimated exposure to SGLT2 inhibitors of 548,565 patient-years of treatment.<sup>1</sup>

Warnings about Fournier's gangrene will be added to the product information for all SGLT2 inhibitors. A [letter has also been sent to advise healthcare professionals](#) of the risk.

Patients taking SGLT2 inhibitors should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area accompanied by fever or malaise.

If Fournier's gangrene is suspected, SGLT2 inhibitor treatment should be stopped and treatment started urgently (including antibiotics and surgical debridement) as appropriate.

### **Background**

SGLT2 inhibitors authorised in the UK include Edistride (dapagliflozin), Forxiga (dapagliflozin), Ebymect (dapagliflozin/metformin), Xigduo (dapagliflozin/metformin), Qtern (dapagliflozin/ saxagliptin), Invokana (canagliflozin), Vokanamet (canagliflozin/metformin), Jardiance (empagliflozin), Synjardy▼ (empagliflozin/metformin), Glyxambi▼ (empagliflozin/linagliptin), Steglatro▼ (ertugliflozin), Segluromet▼ (ertugliflozin/metformin) and Steglujan▼ (ertugliflozin/sitagliptin).

### **Report suspected drug reactions on a Yellow Card**

Please continue to report suspected adverse drug reactions (ADRs) associated with SGLT2 inhibitors on a Yellow Card.

Reporting suspected ADRs, even those known to occur in association with the medicine, adds to knowledge about the frequency and severity of these reactions and can be used to identify patients who are most at risk. Your report helps the safer use of medicines.

Healthcare professionals, patients, and caregivers can report suspected ADRs via the [Yellow Card website](#) or via the Yellow Card app. Download the app today via [iTunes Yellow Card](#) for iOS devices or via [PlayStore Yellow Card](#) for Android devices.

<sup>1</sup>Data derived from IQVIA MIDAS Q4 2012 to Q3 2018, by the MHRA, January 2019: canagliflozin - data available from Q1 2014; dapagliflozin - data available from Q4 2012; empagliflozin – data available from Q3 2014; ertugliflozin - no data available for newly licensed product (Q=Quarter). Patient-years estimated from the data by using defined daily doses (DDD) as provided by WHO.

*Article citation: Drug Safety Update volume 12, issue 7: February 2019: 3.*

## Letters and drug alerts sent to healthcare professionals in January 2019

### **Lartruvo ▼ (olaratumab): no new patients to be prescribed due to study showing no clinical benefit**

In January 2019, [a letter was sent to prescribers and dispensers of Lartruvo](#), indicated for advanced soft tissue sarcoma, to announce that, following the results of a clinical trial (ANNOUNCE) showing no survival benefit:

- no new patients should be prescribed Lartruvo.
- while further assessment of the study results is ongoing, treatment with Lartruvo may continue in patients who experience clinical benefit

Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin. Continued approval is contingent upon verification of clinical benefit in the confirmatory trial ANNOUNCE.

The global phase 3 study (ANNOUNCE) of Lartruvo in combination with doxorubicin in patients with advanced or metastatic soft tissue sarcoma (STS) did not show benefit in terms of survival and progress-free survival compared with doxorubicin, a standard of survival care treatment. See the [letter](#) for the study data.

### **Other letters sent to healthcare professionals**

In January 2019, the below letters were also sent to healthcare professionals:

- [Sodium-Glucose-Co-Transporter 2 inhibitors \(SGLT2i\): risk of Fournier's gangrene \(necrotising fasciitis of the perineum\)](#)
- [Supply of Standard Export pack of Quadrivalent Influenza Vaccine \(split virion, inactivated\) suspension for injection in a pre-filled syringe PL 46602/0017 - Lot R3J824V, Expiry 31/08/2019 – Single Packs](#)
- [Carbimazole or thiamazole \(synonym: methimazole\)-containing products: \(1\) risk of acute pancreatitis and \(2\) strengthened advice on contraception](#)

### **Drug alerts**

- [Class 2 Medicines Recall: Actavis Group PTC EHF - recall of batches of Irbesartan/Hydrochlorothiazide 300/12.5mg Film-coated Tablets and Irbesartan/Hydrochlorothiazide 150/12.5mg Film-coated Tablets.](#) Issued 3 January 2019. Actavis Group PTC EHF is recalling the below batches from pharmacies as a precautionary measure due to possible contamination with N-nitrosodiethylamine (NDEA).
- [Class 2 Medicines Recall: Macleods Pharma UK Limited - Irbesartan 150mg Film-coated tablets, PL 34771/0079 \(MDR 94-06/18\).](#) Issued 21 January 2019. Macleods Pharma UK Limited is recalling the below batches from pharmacies as a precautionary measure due to possible contamination with N-nitrosodiethylamine (NDEA).

*Article citation: Drug Safety Update volume 12, issue 7: February 2019: 4.*

## Medical Device Alerts issued in January 2019

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see [Alerts and recalls for drugs and medical devices](#).

The following alerts were recently issued:

- [FreeStyle Libre flash glucose sensor – Use of barrier methods to reduce skin reactions to the sensor adhesive \(MDA/2019/003\)](#). Issued 29 January 2019. Manufactured by Abbott – some users who are experiencing an immune response (including skin hypersensitivity reactions) to the adhesive are applying creams, patches, or sprays under their sensor to reduce skin reactions, which may affect device performance.

**Actions given in the [alert](#):**

- Identify patients who have reported or may be experiencing skin reactions to their glucose sensor, which may include erythema, itching, and blistering
  - Consider if continued use of this device for patients with skin reactions is suitable.
  - Consider use of alternative glucose monitoring systems for these patients.
- 
- [Arjo Minstrel passive floor lift \(portable hoist\) – risk of spreader bar detachment from lifts without a scale \(MDA/2019/004\)](#). Issued 30 January 2019. Manufactured by ArjoHuntleigh AB – spreader bar may detach from the lift arm during patient transfer with the potential for serious injuries to the patient.

*Article citation: Drug Safety Update volume 12, issue 7: February 2019: 5.*

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