

Drug Safety Update



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

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The Medicines and Healthcare products Regulatory Agency is the government agency which is 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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This month, we inform you that serious and life-threatening cases of diabetic ketoacidosis have been reported in patients taking sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin or empagliflozin). Test for raised ketones in patients with acidosis symptoms, even if plasma glucose levels are near-normal—see article 1.

The increase in cardiovascular risk associated with high-dose ibuprofen (≥ 2400 mg of ibuprofen per day) is similar to that seen with COX-2 inhibitors and diclofenac. Following an EU-wide review, the existing warnings for high-dose ibuprofen have been clarified and strengthened. Avoid giving high-dose ibuprofen to patients with certain established cardiovascular diseases—see article 2.

Use of intrauterine contraception can rarely result in perforation of the uterus. The European Active Surveillance Study for Intrauterine Devices (EURAS-IUD) showed that the most important risk factors for perforation are insertion during lactation and insertion in the 36 weeks after giving birth. Before inserting an intrauterine contraceptive system or device, inform women of the risk and the symptoms of perforation—see article 3.

We invite you to complete our survey on how we communicate medicines safety issues. It will take no more than 15 minutes to complete and your answers will be used to help optimise regulatory safety communications—see article 4.

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1 SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin): risk of diabetic ketoacidosis

Test for raised ketones in patients with acidosis symptoms, even if plasma glucose levels are near-normal.

When treating patients who are taking an SGLT2 inhibitor (canagliflozin, dapagliflozin or empagliflozin):

- test for raised ketones in patients with symptoms of diabetic ketoacidosis (DKA); omitting this test could delay diagnosis of DKA
- if you suspect DKA, stop SGLT2 inhibitor treatment
- if DKA is confirmed, take appropriate measures to correct the DKA and to monitor glucose levels
- inform patients of the symptoms and signs of DKA (see below); advise them to get immediate medical help if these occur
- be aware that SGLT2 inhibitors are not approved for treatment of type 1 diabetes
- please continue to report suspected side effects to SGLT2 inhibitors or any other medicines on a Yellow Card www.gov.uk/yellowcard

Reports of diabetic acidosis

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are licensed for use in adults with type 2 diabetes to improve glycaemic control. Serious and life-threatening cases of DKA have been reported in patients taking SGLT2 inhibitors (canagliflozin, dapagliflozin or empagliflozin).

In several cases, blood glucose levels were only moderately elevated (eg <14 mmol/L or 250 mg/dL), which is **atypical for DKA**. This atypical presentation could delay diagnosis and treatment. Therefore inform patients of the signs and symptoms of DKA (eg nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness) and test for raised ketones in patients with these signs and symptoms.

Half of the cases occurred during the first 2 months of treatment. Some cases occurred shortly after stopping the SGLT2 inhibitor.

One third of the cases involved off-label use in patients with type 1 diabetes. We remind you that this drug class is **not licensed** for the treatment of type 1 diabetes.

The underlying mechanism for SGLT2 inhibitor-associated DKA has not been established. We are investigating this concern along with other EU medicines regulators. We will communicate further advice as appropriate once the investigation is complete.

SGLT2 inhibitors – medicines in this class

The SGLT2 inhibitors marketed in the UK are listed below. Click on the brand name to see the summary of product characteristics (SPC).

Brand name	Active substance(s)
Forxiga ▼	Dapagliflozin tablets (5 mg and 10 mg)
Xigduo ▼	Dapagliflozin/metformin tablets (5 mg/850 mg and 5 mg/1000 mg)
Invokana ▼	Canagliflozin tablets (100 mg and 300 mg)
Vokanamet ▼	Canagliflozin/metformin tablets (50 mg/850 mg, 50 mg/1000 mg, 150mg/850mg, 150mg/1000mg)
Jardiance ▼	Empagliflozin tablets (10 mg and 25 mg)

Further information
[European Medicines Agency announcement](#) June 2015

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2 High-dose ibuprofen (≥ 2400 mg/day): small increase in cardiovascular risk

EU review confirms that the cardiovascular risk of high-dose ibuprofen (≥ 2400 mg/day) is similar to COX-2 inhibitors and diclofenac.

When prescribing or dispensing ibuprofen:

- avoid use of high-dose ibuprofen (≥ 2400 mg per day) in patients with established:
 - ischaemic heart disease
 - peripheral arterial disease
 - cerebrovascular disease
 - congestive heart failure (New York Heart Association [NYHA] classification II-III)
 - uncontrolled hypertension
- review the treatment of patients with the above conditions who are taking high-dose ibuprofen at their next routine appointment
- carefully consider the benefits and risks before starting long-term ibuprofen treatment for patients with significant risk factors for cardiovascular events (eg hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses are required
- we remind you that ibuprofen is contraindicated in patients with severe heart failure
- consider that these recommendations also apply to dexibuprofen (a high dose of dexibuprofen is 1200 mg or more per day, which is equivalent to 2400 mg of ibuprofen)
- consider that no increase in cardiovascular risk is seen with ibuprofen at doses up to 1200 mg per day (the highest dose available over the counter) compared with not taking ibuprofen

Ibuprofen is a non-selective anti-inflammatory drug (NSAID). NSAIDs have long been known to be associated with a small increase in risk of heart attack and stroke.

High-dose ibuprofen and cardiovascular risks

The MHRA and other EU medicines regulators have reviewed the safety of high-dose ibuprofen, following the publication of a meta-analysis of clinical trial data.¹ This meta-analysis showed that people taking ≥ 2400 mg of ibuprofen per day are at a higher risk of arterial thrombotic events (heart attack, stroke) than people taking placebo. The review confirmed that this higher risk is similar to that seen with COX-2 inhibitors and diclofenac.

No increased risk of arterial thrombotic events is seen with ibuprofen at doses up to 1200 mg per day (the highest dose available over the counter) compared with not taking ibuprofen. There are limited data on the risk with ibuprofen at doses between 1200 mg and 2400 mg per day. It is uncertain whether such doses are associated with an increased cardiovascular risk compared with not taking ibuprofen.

In 2013, less than 1% of all prescriptions for ibuprofen in primary care in the UK were for 2400 mg per day or more.

Possible interaction between ibuprofen and low-dose aspirin

The European review also considered the latest data on the possible interaction between ibuprofen and low-dose aspirin. The latest experimental data confirm previous findings that ibuprofen competitively inhibits the effect of low-dose aspirin on platelet aggregation *in vivo*, *ex vivo* and *in vitro*. It is uncertain if these data can be extrapolated to the clinical situation, and clinical data do not support a clinically meaningful interaction. However, the possibility that long term, daily use of ibuprofen might reduce the cardioprotective effects of low-dose aspirin cannot be excluded.

Occasional ibuprofen use is unlikely to have a clinically meaningful effect on the benefits of low-dose aspirin.

1. Coxib and traditional NSAID Trialists' (CNT) Collaboration. 'Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials' *Lancet* 2013; volume 382, pages 769–779

Reminder of existing advice for all NSAIDs

When prescribing any NSAID, we remind you:

- to base the [decision to prescribe](#) an NSAID on an assessment of a patient's individual risk factors, including any history of cardiovascular and gastrointestinal illness
- that naproxen and low-dose ibuprofen (≤ 1200 mg per day) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs
- to use the lowest effective dose for the shortest duration necessary to control symptoms and re-evaluate the patient's need for symptomatic relief and response to treatment periodically

Further information
[European Medicines Agency announcement](#) May 2014

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3 Intrauterine contraception: uterine perforation—updated information on risk factors

The most important risk factors for uterine perforation are insertion during lactation and insertion in the 36 weeks after giving birth. Before inserting an IUS or IUD, inform women of the risk and the symptoms of perforation.

Before inserting an IUS or IUD, inform women that perforation occurs in less than 1 in 1,000 women and that the symptoms include:

- severe pelvic pain after insertion (worse than period cramps)
- pain or heavy bleeding after insertion which continues for more than a few weeks
- sudden changes in periods
- pain during sex
- not being able to feel the threads

Explain to women how to check their threads and tell them to return for a check-up if they cannot feel them (especially if they also have significant pain). Partial perforation may have occurred even if the threads can still be seen; consider this if there is severe pain following insertion.

Intrauterine contraception includes levonorgestrel-releasing intrauterine systems (IUSs) and copper intrauterine devices (IUDs).

IUSs are licensed for several gynaecological conditions including:

- long-term contraception (Jaydess, Levosert, Mirena)
- heavy menstrual bleeding (Levosert, Mirena)
- protection from endometrial hyperplasia during oestrogen replacement therapy (Mirena)

IUDs are used for long-term contraception.

Use of intrauterine contraception can rarely result in uterine perforation. Perforation most often occurs during insertion, but might not be detected until some time later. We have received 114 Yellow Card reports of uterine perforation and 22 reports of devices becoming embedded in the uterus, cervix or other local tissues in association with use of levonorgestrel-releasing IUSs up to 12 February 2015.

1. Heinemann K and others. 'Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices' Contraception 2015; Volume 91, Issue 4, pages 274–279

EURAS-IUD study

The European Active Surveillance Study for Intrauterine Devices (EURAS-IUD) was an observational study which examined the risk of uterine perforation with intrauterine contraception.¹ The study followed 43,078 women who used levonorgestrel-releasing IUSs and 18,370 women who used copper IUDs.

Results

The risk of perforation was increased in the following instances (see table):

- in women who were lactating (compared with women not lactating) at the time of insertion
- when the IUS or IUD was inserted up to 36 weeks (compared with more than 36 weeks) after giving birth

These risk factors were independent of the type of intrauterine contraception inserted.

Table: Incidence of perforation per 1,000 insertions for the entire study cohort (IUS and IUD), stratified by lactation and time since delivery at insertion

	Lactating at time of insertion	Not lactating at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 (95% CI 3.9-7.9; n=6047 insertions)	1.7 (95% CI 0.8-3.1; n=5927 insertions)
Insertion > 36 weeks after delivery	1.6 (95% CI 0.0-9.1; n=608 insertions)	0.7 (95% CI 0.5-1.1; n=41,910 insertions)

CI: confidence interval, IUS: levonorgestrel-releasing intrauterine system, IUD: copper intrauterine device, n: number

Benefits still outweigh the risk

The benefits of intrauterine contraception still strongly outweigh the rare risk of perforation for most women, including those who are lactating or have recently given birth. Therefore we have not put in place any new restrictions on use of intrauterine contraception based on the study findings. The summaries of product characteristics and patient information leaflets have been updated with the information in this article.

Further information

[Letter](#) sent to healthcare professionals in June 2015

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4 Survey of medicines safety communications

Please complete our survey on how we communicate medicines safety issues.

This [survey](#) examines:

- your experience of regulatory safety communications
- your views on their effectiveness
- which information channels you prefer

It is part of an EU-wide project called [SCOPE \(Strengthening Collaboration for Operating Pharmacovigilance in Europe\)](#). This project aims to help medicines regulatory agencies including the MHRA fulfil the requirements of pharmacovigilance legislation introduced in 2012. Your answers will be used to help optimise regulatory safety communications.

This survey is anonymous and will take roughly 15 minutes to complete. We will not use your name if we publish the survey results. If you would like to receive a copy of the publication please fill in your e-mail address on the final page.

To access the survey, click [here](#).

We greatly appreciate your time and opinions.

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5 Hormonal pregnancy tests and birth defects: call for evidence

We have launched a public call for any evidence considered relevant to a possible association between the use of oral hormonal pregnancy tests, which were available until the late 1970s, and adverse effects on pregnancy or birth defects. A group of independent experts will review all evidence provided and we will publish a report of the group's findings. See further information about this consultation, which closes on 30 June 2015, [here](#).

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