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 would like to inform you of a signal of increased lower limb amputation (primarily of the toe) in people taking canagliflozin compared with placebo in a clinical trial involving high cardiovascular risk patients. This signal is under investigation by the European Medicines Agency. Follow standard guidance on foot care in diabetic patients and consider stopping canagliflozin if a patient develops a significant lower limb complication, at least until the condition has resolved – see page 2 for further details.

We would also like to inform you that there have been rare reports of Nexplanon implants having reached the lung via the pulmonary artery. See page 4 for updated instructions on how to correctly insert the implant, and advice on what to do if the implant cannot be palpated.

Finally, we would like to remind you that topical miconazole, including the oral gel, can enhance the anticoagulant effect of warfarin, with potentially serious consequences. If miconazole and warfarin are used concurrently, the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced – see page 6 for further details.

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Canagliflozin (Invokana▼, Vokanamet▼): signal of increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients

A signal of increased lower limb amputation (primarily of the toe) in people taking canagliflozin compared with placebo in a clinical trial in high cardiovascular risk patients is currently under investigation.

Advice for healthcare professionals:

- As a precaution, consider stopping canagliflozin if a patient develops a significant lower limb complication (eg, skin ulcer, osteomyelitis, or gangrene), at least until the condition has resolved, and continue to monitor the patient closely
- carefully monitor patients receiving canagliflozin who have risk factors for amputation (eg, previous amputations, existing peripheral vascular disease, or neuropathy)
- monitor all patients for signs and symptoms of water or salt loss; ensure patients stay sufficiently hydrated to prevent volume depletion in line with recommendations in the product information;[1,2] note that diuretics can exacerbate dehydration
- advise patients to:
  - stay well hydrated
  - carry out routine preventive foot care
  - seek medical advice promptly if they develop skin ulceration, discolouration, or new pain or tenderness
- start treatment for foot problems (eg, ulceration, infection, or new pain or tenderness) as early as possible
- continue to follow standard treatment guidelines for routine preventive foot care for people with diabetes

1 Invokana▼ (canagliflozin) summary of product characteristics, Section 4.4 Special warnings and precautions for use: Use in patients at risk for adverse reactions related to volume depletion (last updated May 2016)
2 Vokanamet▼ (canagliflozin and metformin) summary of product characteristics, Section 4.4 Special warnings and precautions for use: Use in patients at risk for adverse reactions related to volume depletion (last updated May 2016)

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Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated in adults with type 2 diabetes mellitus to improve glycaemic control when diet and exercise alone do not provide adequate glycaemic control. Canagliflozin is given as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Canagliflozin can also be given as add-on therapy with other glucose-lowering drugs, including insulin, when these do not provide adequate glycaemic control.

The canagliflozin-containing medicines marketed in the UK are Invokana▼ (canagliflozin) and Vokanamet▼ (canagliflozin and metformin).

CANVAS trial

The incidence of lower limb amputation (primarily of the toe) is higher in the canagliflozin groups compared with the placebo group in a clinical trial of high cardiovascular risk patients (CANVAS, an on-going long-term cardiovascular outcomes trial). The trial is fully enrolled with 4,330 randomised participants. The mean and median follow-up time is approximately 4.5 years.

The incidence of lower limb amputation is 7 per 1000 patient-years in the canagliflozin 100 mg group and 5 per 1000 patient-years in the canagliflozin 300 mg group, compared with 3 per 1000 patient-years in the placebo group.

This increased risk was observed independent of risk factors. However, the absolute risk was higher in patients with previous amputations, existing peripheral vascular disease, or neuropathy. No dose response was observed.

Any possible mechanism behind these events is as yet unknown. However, dehydration and volume depletion might increase this risk. We therefore recommend that you follow the interim advice outlined above while this signal is being investigated by the European Medicines Agency. The results of the review will be communicated when available.

Other trials: no significantly increased risk observed

In an ongoing outcome trial with a similar population to CANVAS, the CANVAS-R trial, there have been 16 amputations in the canagliflozin group and 12 amputations in the placebo group. The estimated annualised incidence of amputations is 7 per 1000 patient-years in the canagliflozin group compared with 5 per 1000 patient-years in the placebo group (no statistically significant difference).

12 completed phase 3 or 4 trials have shown no increase in amputation incidence with canagliflozin (incidence of 0.6 per 1000 patient-years in canagliflozin groups and 2 per 1000 patient-years in control groups; mean follow-up of 0.9 years).

Reporting of suspected adverse reactions

Suspected side effects to canagliflozin or any other medicine should be reported to us on a Yellow Card.

Further information

NICE guideline on diabetic foot problems: prevention and management

Letter sent to health professionals, April 2016

European Medicines Agency statement, April 2016

Article citation: Drug Safety Update volume 9 issue 11 June 2016: 1

Nexplanon (etonogestrel) contraceptive implants: reports of device in vasculature and lung

There have been rare reports of Nexplanon implants having reached the lung via the pulmonary artery. An implant that cannot be palpated at its insertion site in the arm should be located as soon as possible and removed at the earliest opportunity. If an implant cannot be located within the arm, perform chest imaging. Correct subdermal insertion reduces the risk of these events.

Updated advice for healthcare professionals:

- An implant should only be inserted subdermally and by a healthcare professional who has been appropriately trained and accredited
- Do not insert over the sulcus (groove) between the biceps and triceps.
- Take care to avoid insertion close to any blood vessels or nerve bundles eg the ulnar nerve
- Immediately after insertion, verify the presence of the implant by palpation
- Show the woman how to locate the implant and advise her to do this frequently for the first few months; if she has any concerns she should return to the clinic for advice
- Locate an implant that cannot be palpated (eg, using imaging of the arm) and remove it at the earliest opportunity
- If an implant cannot be located in the arm by palpation or imaging, perform chest imaging
- Surgical or endovascular procedures may be required to remove an implant from the chest
- Review the updated instructions on how to correctly insert the implant, including an amended diagram that illustrates:
    - the correct angle on the arm for insertion
    - how to view the needle to avoid deep insertion

Nexplanon is a highly effective, long-acting contraceptive implant which contains the active ingredient etonogestrel, a synthetic progestogen. Nexplanon acts by preventing ovulation and is usually effective for 3 years. Safety and efficacy have been established in women between 18 and 40 years old. For maximum effectiveness Nexplanon needs to be correctly implanted by someone who is trained to fit it.

Reports and potential risk factors

There have been rare reports of Nexplanon implants having reached the lung via the pulmonary artery. The number of reports of Nexplanon implants in the vasculature received by the licence-holder is estimated to be approximately 1.3 per million implants sold worldwide.

No definitive set of adverse reactions have been associated with these events. However some cases have reported:

- dyspnoea
- haematoma at the insertion site
- excessive bruising at the insertion site
- a combination of the above

No specific risk factors have been identified. Potential risk factors include:

- deep insertion
- insertion in an inappropriate site
- insertion in thin arms

Evidence from the literature shows that implants found in the vasculature can become endothelised into the pulmonary artery.[1-3] If they are located early enough it is possible to remove them by an endovascular procedure.[4-5] Women should therefore be shown how to locate the implant immediately following insertion and advised to check the position of the implant frequently for the first few months.

1 D'Journo XB, et al. Intravascular pulmonary migration of a subdermal contraceptive implant. Ann Thorac Surg 2015; 99: 1828.
2 Patel A, et al. Contraceptive implant embolism into the pulmonary artery. Ann Thorac Surg 2014; 97: 1452.
3 O'Brien A, et al. Subdermal contraceptive implant embolism to a pulmonary artery. Ann Thorac Surg 2015; 2254–55.
4 Heudes P-M, et al. Migration of a contraceptive subcutaneous device into the pulmary artery. Report of a case. Case Reports in Women's Health 2015; 8: 6–8.
5 Maroteix P, et al. Embolie pulmonaire par implant progestatif [Pulmonary embolus with a progestogen implant]. Ann Fr Med Urgence 2015; 5: 332–33.

Expert removers' network

A network of healthcare professionals who are experienced in implant localisations and difficult removals is available for consultation. To request additional information on implant insertion and removal, contact the network by calling 01992 467272.

Reporting of suspected adverse reactions

Report any suspected side effects to Nexplanon, or any other medicine or medical device, to us on a Yellow Card, including difficulties with insertion or removal of Nexplanon.

Further information:
Nexplanon product information

Letter sent to healthcare professionals in May 2016

Article citation: Drug Safety Update volume 9 issue 11 June 2016: 2

Topical miconazole, including oral gel: reminder of potential for serious interactions with warfarin

In view of reports of serious bleeding events in patients taking miconazole and warfarin, we are considering further measures to minimise the risk of potentially serious interactions between miconazole and warfarin.

Reminder for healthcare professionals:

- Miconazole, including the topical gel formulation, can enhance the anticoagulant effect of warfarin—if miconazole and warfarin are used concurrently, the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced
- Patients should be advised to tell their doctor or pharmacist if they are receiving warfarin before using products that contain miconazole (including those available without prescription), and to seek medical advice if they notice signs of over-anticoagulation during treatment, such as sudden unexplained bruising, nosebleeds or blood in the urine

Miconazole (Daktarin, Daktacort) is an antifungal indicated for prevention and treatment of various infections of the mouth, throat, skin, nails, or genitals. It is usually applied topically as a cream, ointment, powder, or oral gel. Some products are available without a prescription.

Warfarin is an oral anticoagulant that has been widely used since the 1950s for prophylaxis of thromboembolic events. Daily dose depends on individual requirements, and patients receiving long-term therapy require regular coagulation tests.

Drug interactions

The potential for drug interactions between miconazole and warfarin is well established.[1–3] The mechanism is understood to be inhibition by miconazole of one of the main cytochrome P450 isozymes involved in warfarin metabolism (CYP2C9), resulting in reduced warfarin clearance and an enhanced anticoagulant effect.

Prescribing information for products that contain miconazole warns that because miconazole inhibits CYP2C9, caution should be exercised for patients on oral anticoagulants such as warfarin, and the anticoagulant effect monitored (warfarin dose reduction may be needed). Patient Information Leaflets for miconazole products advise users to tell their doctor or pharmacist if they are taking warfarin.

Yellow Card reports

Up to 13 April 2016, we have received 146 Yellow Cards that report possible drug interactions between miconazole and warfarin. Most reports (128,88%) concerned the oral gel form of miconazole.

The most frequently reported events were: increased international normalised ratio (INR, 111 reports); contusion (21); haematuria (17); and epistaxis (8).

1 Stockley I. Drug interaction with coumarin derivative anticoagulants. Br Med J 1982; 285: 1044–45.
2 Ariyaratnam S, et al. Drug points: Potentiation of warfarin anticoagulant activity by miconazole oral gel. BMJ 1997; 314: 349.
3 Filmer S. Warfarin and oral miconazole: a major interaction overlooked in practice. The Pharmaceutical Journal,1 April 2012.

Approximately half of the 146 cases reported an INR increase above 10—ie, the patient was at significantly increased risk of bleeding events (noting that the target INR range for a patient on long-term warfarin therapy is usually between 2 and 3). In 3 cases, a fatal outcome was reported as a result of a haemorrhagic event.

Latest MHRA review

We are currently reviewing available data for this interaction to determine whether further measures are required to minimise the risks to patients. This review follows a coroner's report of a death, which may have been partly due to the coadministration of miconazole oral gel and warfarin. Further advice will be communicated as appropriate when the review is complete.

Suspected drug interactions between miconazole and warfarin should be reported to us on a Yellow Card.

Further information

NHS Wales Patient Safety Notice. Risk of patient harm from an interaction between miconazole and coumarin anticoagulants, May 2016.

Article citation: Drug Safety Update volume 9 issue 11 June 2016: 3

Letters sent to healthcare professionals in May 2016

In May 2016, letters were sent regarding:

- Nexplanon (etonogestrel) implants have been found rarely in the vasculature and lung: an update regarding possible risks and complications regarding insertion, localisation and removal (sent 31 May 2016)—see also article in this issue
- ERWINASE: notice of special handling instructions—vials of ERWINASE from batch 174g should be used with a 5-micron filter needle (sent 4 May 2016)

Article citation: Drug Safety Update volume 9 issue 11 June 2016: 4