20/04/2017
EMA/118223/2017

SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information

Diabetes patients reminded of importance of preventative foot care

On 24 February 2017, the European Medicines Agency (EMA) informed about a potential increased risk of lower limb amputation (mostly affecting the toes) in patients taking the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes.

Patients taking these medicines are reminded to check their feet regularly and follow their doctor's advice on routine preventative foot care. They should also tell their doctor if they notice any wounds or discoloration, or if their feet are tender or painful.

The review of SGLT2 inhibitors was prompted by an increase in lower limb amputations (mostly affecting the toes) in patients taking canagliflozin in two clinical trials, CANVAS and CANVAS-R. The studies involved patients at high risk of heart problems and compared canagliflozin with placebo (a dummy treatment).

All patients with diabetes (especially those with poorly controlled diabetes and problems with the heart and blood vessels) are at higher risk of infection and ulcers (sores) which can lead to amputations. The mechanism by which canagliflozin may increase the risk of amputation is still unclear.

An increase in lower limb amputations has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin. However, data available to date are limited and the risk may also apply to these other medicines.

Further data are expected from ongoing studies with canagliflozin, dapagliflozin and empagliflozin.

A warning of the potential increased risk of toe amputation has been included in the prescribing information for these medicines. For canagliflozin, the prescribing information also lists lower limb amputation as an uncommon side effect (occurring in between 1 and 10 patients in 1,000). Doctors may consider stopping treatment with canagliflozin if patients develop significant foot complications such as infection or skin ulcers.

The review of SGLT2 inhibitors was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were endorsed by the Committee for Medicinal Products for Human Use (CHMP) and sent to the European Commission, which issued a final legally-binding decision valid throughout the EU.

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Information for patients

- The diabetes medicine canagliflozin may increase the risk of lower limb amputation (mostly affecting the toes).
- The risk of lower limb amputation with canagliflozin may also apply to other diabetes medicines in the same class, dapagliflozin and empagliflozin.
- All patients with diabetes are at increased risk of infection and sores which can lead to amputations. It is currently not known how canagliflozin may increase the risk of toe amputation.
- If you are taking medicines containing canagliflozin, dapagliflozin and empagliflozin to treat your type 2 diabetes, it is particularly important that you check your feet regularly and follow your doctor's advice on routine preventative foot care and adequate hydration.
- Tell your doctor about any wounds or discoloration, or if your feet are tender or painful.
- If you have any questions or concerns about your treatment, speak to your doctor, pharmacist or nurse.

Information for healthcare professionals

- An increase in lower limb amputation (mostly affecting the toes) has been observed in two long-term clinical trials, CANVAS and CANVAS-R, in patients taking canagliflozin compared with those taking placebo. The studies, which are still ongoing, involved patients at high cardiovascular risk.
- Although an increase in amputations has not been seen in studies with other SGLT2 inhibitors, dapagliflozin and empagliflozin, data available to date are limited and the risk may also apply to these other medicines.
- The underlying mechanism by which canagliflozin may increase the risk of amputation has not been established and no risk factors apart from general risk factors for amputation have been identified.
- As a precaution, patients taking an SGLT2-inhibitor should be counselled about the importance of routine preventative foot care.
- For canagliflozin, consideration should also be given to carefully monitoring patients at higher risk of amputation and counselling them about the importance of maintaining adequate hydration.
- Consideration may be given to stopping treatment with canagliflozin in patients who develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

Information about the CANVAS and CANVAS-R studies

CANVAS (CANagliflozin cardioVascular Assessment Study) is a long-term study to look at whether canagliflozin reduces cardiovascular (heart and blood vessels) disease. It compared the effects of canagliflozin and placebo (a dummy treatment) together with standard of care in diabetes patients at high risk of heart problems. CANVAS was authorised between 2009 and 2010 in the following EU countries: Belgium, Czech Republic, Estonia, France, Germany, Hungary, Luxemburg, Netherlands, Norway, Poland, Spain, Sweden and United Kingdom.

As of September 2016, the incidence of lower limb amputation (mostly affecting the toes) in the CANVAS study was 7 in 1,000 patient-years with canagliflozin 100 mg daily and 5 in 1,000 patient-

years with canagliflozin 300 mg daily, compared with 3 in 1,000 patient-years with placebo. (One patient-year is equivalent to 1 patient taking the medicine for 1 year.) The study enrolled around 4,300 patients.

The CANVAS-R study is a study with a similar population to CANVAS. The purpose of this study was to assess the effect of canagliflozin compared with placebo on progression of albuminuria (presence of albumin in the urine, which is an early sign of kidney disease) in patients with type 2 diabetes receiving standard of care but whose blood sugar is not well controlled and who are at increased risk of cardiovascular disease. CANVAS-R was authorised in the following EU countries: Belgium, Czech Republic, France, Germany, Hungary, the Netherlands, Poland, Spain, Sweden, and United Kingdom.

As of September 2016, the incidence of lower limb amputation was 8 in 1,000 patient-years with canagliflozin and 4 in 1,000 patient-years with placebo. The study enrolled over 5,800 patients.

The incidences of lower limb amputation given above for both CANVAS and CANVAS-R are based on interim data, and final incidence rates will depend on analysis of the final study datasets.

More about the medicines

Canagliflozin, dapagliflozin and empagliflozin are type 2 diabetes mellitus medicines of the class sodium-glucose co-transporter-2 (SGLT2) inhibitors. They block a protein in the kidneys called SGLT2, which absorbs glucose back from the urine into the bloodstream as the blood is filtered in the kidneys. By blocking the action of SGLT2, these medicines cause more glucose to be lost in the urine, thereby reducing the levels of glucose in the blood.

This review covered the following medicines containing SGLT2 inhibitors: Ebymect (dapagliflozin / metformin), Edistride (dapagliflozin), Forxiga (dapagliflozin), Invokana (canagliflozin), Jardiance (empagliflozin), Synjardy (empagliflozin / metformin), Vokanamet (canagliflozin / metformin) and Xigduo (dapagliflozin / metformin).

More information on these medicines can be found on EMA's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

More about the procedure

The review of canagliflozin was initiated at the request of the European Commission on 15 April 2016, under Article 20 of Regulation (EC) No 726/2004. The review was extended to include the other medicines in the same class, dapagliflozin and empagliflozin, on 7 July 2016.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion was be forwarded to the European Commission, which issued a final legally binding decision applicable in all EU Member States.

Commission Decision date for Edistride, Forxiga, Invokana, Jardiance, Synjardy, Vokanamet and Xigduo: 20/04/2017

Commission Decision date for Ebymect: 04/05/2017