



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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PRAC concludes that diabetes medicine canagliflozin may contribute to risk of toe amputation

Risk may also apply to other medicines in the same class

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is warning that an increase in cases of lower limb amputation (mostly affecting the toes) has been observed in patients taking the type 2 diabetes medicine canagliflozin compared with those taking placebo (a dummy treatment) in two clinical trials, CANVAS and CANVAS-R. The studies, which are still ongoing, involved patients at high risk of heart problems.

Patients with diabetes (especially those with poorly controlled diabetes and pre-existing problems with the heart and blood vessels) are at increased 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 increased risk 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.

On the basis of the available data, the PRAC recommends that a warning on the risk of lower limb amputation (mostly affecting the toes) should be included in the prescribing information for these medicines, highlighting the importance of routine preventative foot care.

For canagliflozin, lower limb amputation should be listed as an uncommon side effect (occurring in between 1 and 10 patients in 1,000). Doctors should consider stopping treatment with canagliflozin if patients develop significant foot complications such as infection or skin ulcers.

The PRAC recommendation will now be sent to EMA's Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion. Further details and advice for patients and healthcare professionals will be published at the time of the CHMP opinion.



More about the medicine

Canagliflozin, dapagliflozin and empagliflozin are type 2 diabetes 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 removed through the urine, thereby reducing the levels of glucose in the blood.

The following medicines containing SGLT2 inhibitors are currently authorised in the EU: Ebymect (dapagliflozin / metformin), Edistride (dapagliflozin), Forxiga (dapagliflozin), Glyxambi (empagliflozin / linagliptin), Invokana (canagliflozin), Jardiance (empagliflozin), Qtern (saxagliptin / dapagliflozin) 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 has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. The PRAC recommendations will now be sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's opinion.

The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.

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