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Update of 8 July 2016:

The scope of the review, which initially only covered canagliflozin, has been extended to include the other medicines in the same class, dapagliflozin and empagliflozin. This is because the potential risk being evaluated for canagliflozin may be relevant for the other medicines in this class.

EMA reviews diabetes medicine canagliflozin

Review follows data on toe amputations in ongoing study

The European Medicines Agency (EMA) has started a review of the diabetes medicine canagliflozin after an increase in amputations, mostly affecting toes, was observed in an ongoing clinical trial called CANVAS.

Cases of lower limb amputation occurred in both the canagliflozin and placebo groups in the trial and the possibility that canagliflozin increases lower limb amputations is currently not confirmed. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has requested more information from the company to assess whether canagliflozin causes an increase in lower limb amputations and whether any changes are needed in the way this medicine is used in the EU.

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 ulceration which can result in lower limb amputations. No increase in such amputations was seen in 12 other completed clinical trials with canagliflozin. A small, non-statistically significant increase in the number of amputations occurred in another ongoing study called CANVAS-R. Both CANVAS and CANVAS-R involve patients at high risk of problems with the heart and blood vessels.

The PRAC will also ask for data on other medicines in the same class known as SGLT2 inhibitors[1]. Based on this, the PRAC may decide to extend the scope of the review to cover these medicines.

[1] SGLT2 inhibitors are canagliflozin, dapagliflozin and empagliflozin.

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While the review on canagliflozin is ongoing, healthcare professionals will receive a letter reminding them about the importance of routine foot care to avoid cuts or sores of the feet and to treat them promptly should they occur to prevent infection and ulceration. Patients at increased risk of amputation (such as those who have had a previous amputation) should be carefully monitored. As a precautionary measure, doctors may consider stopping treatment with canagliflozin in patients who develop significant foot complications.

Patients who have any questions should speak to their doctor or pharmacist. It is important that patients with diabetes continue to take their prescribed treatment and do not stop treatment without first consulting a healthcare professional.

More about the medicine

Canagliflozin is the active substance in two centrally authorised diabetes medicines, Invokana and Vokanamet (which also contains metformin), approved in the EU in 2013 and 2014, respectively.

Canagliflozin is an SGLT2 inhibitor. It works by blocking a protein in the kidneys called sodium glucose co-transporter 2 (SGLT2). SGLT2 absorbs glucose back into the bloodstream as the blood is filtered in the kidneys. By blocking the action of SGLT2, canagliflozin causes more glucose to be removed via the urine, thereby reducing glucose in the blood.

The other SGLT2 inhibitors are dapagliflozin and empagliflozin.

More 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 compares the effects of canagliflozin and placebo (a dummy treatment) together with standard 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.

The incidence of lower limb amputation in the study is currently 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. Patients in the study have so far been followed up for an average of 4.5 years.

The CANVAS-R study is an ongoing study with a similar population to CANVAS. In this trial, the incidence of lower limb amputation is 7 in 1,000 patient-year with canagliflozin and 5 in 1,000 patient-years with placebo. This difference is not statistically significant. Patients in this study have so far been followed up for an average of 0.75 years.

The Independent Data Monitoring Committee for CANVAS and CANVAS-R has recommended that the trials should continue.

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 is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the committee responsible for the evaluation of safety issues for human medicines, which will make a set of recommendations.

The PRAC recommendations will then be forwarded to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt an 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.