7 July 2016
EMA/PRAC/472827/2016

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for dapagliflozin and empagliflozin containing medicinal products

Referral under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

SGLT2 inhibitors and lower limb amputation (canagliflozin, dapagliflozin, empagliflozin)

INVOKANA (canagliflozin) EMEA/H/A-20/1442/C/2649/0018

VOKANAMET (canagliflozin / metformin) EMEA/H/A-20/1442/C/2656-0014

FORXIGA (dapagliflozin) EMEA/H/A-20/1442/C/2322/0029

EDISTRIDE (dapagliflozin) EMEA/H/A-20/1442/C/4161/0010

XIGDUO (dapagliflozin/metformin) EMEA/H/A-20/1442/C/2672/0024

EBYMECT (dapagliflozin/metformin) EMEA/H/A-20/1442/C/4162/0013

JARDIANCE (empagliflozin) EMEA/H/A-20/1442/C/2677/0023

SYNJARDY (empagliflozin/metformin) EMEA/H/A-20/1442/C/3770/0022

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1. Background

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are used together with diet and exercise in patients with type 2 diabetes, either alone or in combination with other diabetes medicines. A review under article 20 of Regulation (EC) No 726/2004 was started by the European Medicines Agency (EMA) in April 2016 for canagliflozin after an increase in amputations, mostly affecting the toes, was observed in an ongoing clinical trial (CANVAS). Separately, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC)also asked for data from other medicinal products from the same class (dapagliflozin and empagliflozin) in order to decide on a possible extension of the scope of the review to cover all SGLT2 medicines. Having considered available data, the PRAC is of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk specific to canagliflozin-containing medicines and different from the other members of the class. Data on amputation events from clinical trials and post-marketing surveillance for dapagliflozin and empagliflozin-containing medicines are either not available to the same extent as for canagliflozin-containing medicines or have some limitations; therefore, the PRAC considered that a class effect cannot currently be excluded.

In view of the above, the PRAC decided at its July 2016 plenary meeting to extend the current procedure to include all of the above mentioned products. The PRAC hereby requests that the marketing authorisation holders (MAHs) for dapagliflozin and empagliflozin containing medicinal products respond to the following questions in writing:

2. Questions

The marketing authorisation holders MAH(s) for dapagliflozin and empagliflozin containing medicinal products are requested to address the following questions:

Amputation events and preliminary stages

Question 1

Data on events of skin ulceration, peripheral ischemia, peripheral vascular disease, gangrene, cellulitis, wound, peripheral arterial occlusive disease, intermittent claudication and other relevant MedDRA Preferred Terms (PTs) for the MedDRA High Level Term (HLT) Skin and subcutaneous tissue ulcerations should be provided for all completed phase 3 and 4 clinical trials, where dapagliflozin or empagliflozin was investigated, by submitting data on the event numbers, the rate of events and the overall numbers of patients in each active and comparison groups and for each of the trials separately (e.g. by providing a table indicating the trial and the event numbers and numbers of patients included in the trial).

Risk factors, mechanisms

Question 2

Please discuss possible mechanisms of action by which SGLT2 inhibitors may increase the risk of amputations including data from clinical studies and published literature concerning your active substances relating to volume depletion, concomitant antidiabetic medication, concomitant use of diuretics and in particular loop diuretics and other possible mechanisms than volume depletion. Discuss the relevance of the mechanisms for your product(s).

Pharmacovigilance measures

Question 3

Please explore possibilities to perform an individual participant meta-analysis including cardiovascular outcome trials and other clinical trials as additional pharmacovigilance measure to address and explore amputation risk.