# Annex IV

## Scientific conclusions

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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.

In March 2016 the EMA was informed by the Marketing authorization holder (MAH) of canagliflozin about an approximately 2-fold increase of lower limb amputations in canagliflozin-treated subjects compared to placebo in the MAH sponsored ongoing cardiovascular (CV) event study CANVAS. In addition, an analysis of the ongoing renal study CANVAS-R with a similar population as CANVAS showed a numerical imbalance with regards to amputation events.

Further to the information received by the EMA, the Independent Data Monitoring Committee (IDMC) for the CANVAS and CANVAS-R studies, which has access to all un-blinded CV outcome and safety data, recommended that the study should continue, that action to minimize this potential risk should be taken and that participants should be informed adequately about this risk.

The European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004 on 15 April 2016; the PRAC was requested to assess the impact on the benefit-risk balance of canagliflozin containing medicinal products, to assess whether this is a class issue and to issue a recommendation by 31 March 2017 on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked and whether provisional measures are necessary to ensure the safe and effective use of these medicinal products.

A Direct Healthcare Professional Communication (DHPC) was circulated on 2 May 2016 to inform healthcare professionals that a two-fold higher incidence of lower limb amputation (primarily of the toe) had been seen in a clinical trial with canagliflozin; in addition, the need to counsel patients about the importance of routine preventative foot care was highlighted. The communication also asked healthcare professionals to consider treatment discontinuation in patients who develop amputation preceding events.

Furthermore, the PRAC considered that a class effect could not be excluded, as all SGLT2 inhibitors share the same mechanism of action, as the potential mechanism leading to an increased amputation risk is not known, and as an underlying cause specific to canagliflozin containing medicines only cannot be identified at the moment. Consequently, the EC requested on 6 July 2016 to extend the current procedure to include all of the authorised products of the class of SGLT2 inhibitors.

### Overall summary of the scientific evaluation by the PRAC

Having considered all available data, the PRAC was of the view that the growing data on amputation in the CANVAS and CANVAS-R trial confirm an increased amputation risk for canagliflozin; it is unlikely that the difference in amputation risk seen with canagliflozin compared to placebo is a finding by chance. The PRAC also considered that 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 here were some limitations in the data collection.

The PRAC was also of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other products of the class. All members of the class share the same mode of action and there is no confirmed underlying mechanism that is canagliflozin-specific. The mechanism of action that would allow understanding which patients are at risk is therefore still unclear.

PRAC noted that an increased amputation risk has only become apparent with canagliflozin so far, but one large cardiovascular outcome study (DECLARE) is still on-going for dapagliflozin and amputation events were not been systematically captured within the completed large cardiovascular outcome study conducted with empagliflozin (EMPA-REG). Hence, it is currently not possible to establish whether the increased amputation risk is a class effect or not.

Therefore, having considered all the data submitted, in view of the above, the PRAC concluded that the benefit-risk balance of the bove listed products remains positive, but considered that changes to the product information of all authorised SGLT2 inhibitors adding information on the risk of lower limb amputations, as well as additional pharmacovigilance activities to be reflected in the RMP, are warranted. The CANVAS and CANVAS-R studies and the CREDENCE and DECLARE Studies are planned to be completed in 2017 and 2020, respectively. Final analysis of these studies, after un-blinding, will provide further information on the benefit/risk of SGLT2 inhibitors particularly of the risk of lower limb amputations.

**Grounds for PRAC recommendation**

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for the products listed in Annex A;
- The PRAC reviewed the totality of the data submitted by the marketing authorisation holders in relation to the risk of lower limb amputation in patients treated with Sodium-glucose co-transporter 2 (SGLT2) inhibitors for type 2 diabetes mellitus;
- The PRAC considered that the available data on amputation in the CANVAS and CANVAS-R trials confirm that treatment with canagliflozin may contribute to an increased risk of amputation of the lower limb, mainly of the toe;
- The PRAC was also of the opinion that a mechanism of action, allowing to understand which patients are at risk, is still unclear;
- The PRAC was of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other products of the class;
- The PRAC noted that 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 there were some limitations in the data collection of these events;
- The PRAC therefore considered that the risk may constitute a possible class effect;
- Because no specific risk factors could be identified apart from general amputation risk factors potentially contributing to the events, the PRAC recommended that patients should be advised on routine preventative foot care and maintaining adequate hydration as a general advice to prevent amputation;
- The PRAC was therefore of the view that the risk of lower limb amputation should be included in the product information for all products listed in Annex A, with a warning highlighting to healthcare professional and patients the importance of routine preventative foot care. The warning for canagliflozin also includes information that, in patients developing amputation

preceding events, consideration may be given to discontinue treatment. For canagliflozin, lower limb amputations (mainly of the toe) have been also included, as an adverse drug reaction, in the product information;

- The PRAC also considered that additional information on amputation events should be collected through appropriate case report forms (CRFs) for clinical trials, follow-up questionnaires for post-marketing cases, use of common MedDRA preferred term (PT) lists for amputation preceding events, and appropriate meta-analyses of large studies including cardiovascular outcome studies. All RMPs should be updated accordingly via an appropriate variation to be submitted no later than one month of the European Commission decision;

The PRAC, as a consequence, concluded that the benefit-risk balance of the SGLT2 inhibitor containing products identified in Annex A remains favourable, subject to the agreed amendments to the product information and additional pharmacovigilance activities to be reflected in the RMP.

The PRAC therefore recommended that the variation to the terms of the marketing authorisation for the above listed products referred to in Annex A, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation, was warranted.

**CHMP opinion**

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

***Overall conclusion***

The CHMP, as a consequence, considers that the benefit-risk balance of Invokana, Vokanamet, Forxige, Edistride, Xigduo, Ebymect, Jardiance and Synjardy remain favourable subject to the amendments to the product information described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Invokana, Vokanamet, Forxige, Edistride, Xigduo, Ebymect, Jardiance and Synjardy.