NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission:

Product Names	INVOKANA (canagliflozin) VOKANAMET (canagliflozin / metformin)
Procedure name	Canagliflozin and lower limb amputation
Active Substance(s)	Canagliflozin containing products
Pharmaceutical form(s)	All
Strength(s)	All
Route of administration(s)	All
Marketing Authorisation Holders	Janssen- Cilag International

Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitors which are used together with diet and exercise in patients with type 2 diabetes (T2DM), either alone or in combination with other diabetes medicines. SGLT2 is expressed in the proximal renal tubules and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By blocking the action of SGLT2, SGLT2 inhibitors cause more glucose to be removed via the urine, thereby reducing the levels of glucose in the blood via an insulin-independent mechanism. Canagliflozin is centrally authorised in Europe as a monocomponent INVOKANA and as fixed-dose combination VOKANAMET (Canagliflozin+ metformin).

In March 2016, the EMA was informed by the marketing authorisation holder of an increased potential risk of lower limb amputations by approximately 2-fold increase in canagliflozin-treated subjects compared to placebo in the MAH sponsored cardiovascular event study CANVAS. CANVAS is an ongoing Phase 3, double-blind, randomised, placebo-controlled, 3-arm, parallel-group, multicentre study to evaluate the effects of canagliflozin on cardiovascular (CV) outcomes in adult subjects with T2DM receiving standard of care but with an inadequate glycaemic control and at an elevated risk of CV events. The majority of the amputations were amputations of the toe. Incidence rates per 1000 patient-years exposure for lower extremity amputations were 7.3 for patients on the arm receiving canagliflozin 100mg, 5.4 for patients receiving canagliflozin 300mg and 3 for patients on placebo. Although no dose-response relationship was seen, the difference between arms was seen early in the study. This increased risk was observed independent of predisposing risk factors, although the absolute risk was higher in patients with previous amputations, existing peripheral vascular disease or neuropathy.

In addition, an analysis of CANVAS-R, an ongoing renal assessment study with a similar population as CANVAS, showed a numerical imbalance with regard to amputation events (16 events in the canagliflozin group and 12 events in the placebo group). The estimated annualised incidence rate of amputations is 7 and 5 events per 1000 patient-year exposure in the canagliflozin and placebo group, respectively with no statistically significant difference. A higher incidence of amputation was not observed across 12 other completed Phase 3/4 clinical trials with a mean follow-up of 0.9 years (0.6/1000 patient-years in canagliflozin and 2/1000 patient-years in control groups).

The EMA was also informed that the Independent Data Monitoring Committee (IDMC) for the CANVAS and CANVAS-R studies, which has access to the unblinded CV outcome and the safety data, recommended that this study should continue and that action to minimise this risk should be taken and the participants informed adequately of this risk.

In view of the need to further investigate this potential risk and the review of all related available data, the European Commission initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance of INVOKANA and VOKANAMET. The European Commission requests the EMA to give its opinion by 31 March 2017 on whether the marketing authorisations of these products should be maintained, varied, suspended or revoked. As the request is based on the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

In addition, the European Commission requests the Agency to give its opinion as to whether provisional measures are necessary to ensure the safe and effective use of these medicinal products.

As all SGLT2 inhibitors share the same mechanism of action and presently the mechanism behind this potential risk is unknown, the PRAC may consider if necessary extending this review to the other SGLT2 inhibitors (dapagliflozin and empagliflozin-containing medicines).). If this is the case, the Agency shall immediately liaise with the European Commission.

Signed [redacted] Date 15/4/2016.
Robert Vanhoorde
Head of Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General