9 February 2017
EMA/PRAC/637349/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC assessment report

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

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

Procedure number(s):

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. Information on the procedure

1.1. Referral of the matter to the PRAC

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 was not known, and as an underlying cause specific to canagliflozin containing medicines only could not be identified. 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.

2. Scientific discussion

2.1. Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors inhibit the SGLT2 transporter responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Inhibiting SGLT2 reduces reabsorption of filtered glucose, lowers the renal threshold for glucose (RTG) and increases urinary glucose elimination, thereby lowering elevated plasma glucose concentrations by an insulin-independent mechanism in patients with type 2 diabetes.

Canagliflozin and dapagliflozin are indicated together with diet and exercise in the treatment of type 2 diabetes mellitus (T2DM) to improve glycaemic control in adults, either alone or in combination with other diabetes medicines as follows:

- Monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.
- Add-on combination therapy, in combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Empagliflozin is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

CANVAS is an ongoing Phase 3, double-blind, randomized, placebo-controlled, 3-arm, parallel-group, multicentre study to evaluate the effects of canagliflozin on 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. Interim analysis of the CANVAS study (cut-off October 2015) showed a potential risk of lower limb amputations by approximately 2-fold increase in canagliflozin-treated subjects compared to placebo. The majority were amputations of the toe. At this time, the incidence of lower limb amputation (mostly affecting the toes) in the CANVAS study was 7.3 in 1,000 patient-years with canagliflozin 100 mg daily and 5.4 in 1,000 patient-years with canagliflozin 300 mg daily, compared with 3 in 1,000 patient-years with placebo. Although no dose-response relationship was seen, the difference between arms was seen early in the study. This increase was observed independent of predisposing risk factors, although the absolute risk was higher in patients with previous amputations, existing peripheral disease or neuropathy.

In addition, CANVAS-R, an on-going renal assessment study with a similar population as CANVAS, showed a numerical imbalance with regards to amputation events (16 events in the canagliflozin group and 12 events in the placebo group). The estimated annualised incidence rate of amputations was 7 and 5 events per 1000 patient-years exposure in the canagliflozin and placebo group, respectively, with no statistically significant difference.

In order to evaluate whether these events were related to canagliflozin specifically or whether they might be a class effect, the PRAC requested the MAHs of all authorised SGLT2 containing medicinal products (as mono-component or combination products), to provide all related available data from finalised and ongoing clinical trials and reports from post-marketing studies.

The PRAC reviewed all available data from clinical studies, published literature and post-marketing experience, including responses submitted by the marketing authorisation holders, as appropriate, on the efficacy and safety of SGLT2 inhibitors in their approved indication. It should be noted that this report summarises only the most relevant data.

Table 1. Overview of key safety data submitted with regard to amputation risk

CANVAS	CV outcomes	In patients with type 2 diabetes mellitus	Phase 3, double-blind, randomized, placebo-controlled, 3-arm, parallel-group, multicenter study	Canagliflozin, placebo	Ongoing
CANVAS-R	Renal outcomes	In patients with type 2 diabetes mellitus	Phase 3, double-blind, randomized, placebo-controlled, 2-arm, parallel-group, multicenter study	Canagliflozin, placebo	Ongoing

CREDENCE	Renal and CV outcomes	In patients with type 2 diabetes and diabetic nephropathy	Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multicentre study	Canagliflozin, placebo	Ongoing
DECLARE	CV outcomes	In patients with 2 diabetes mellitus	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	Dapagliflozin, placebo	Ongoing
EMPA-REG	CV outcomes	In patients with 2 diabetes mellitus	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	Empagliflozin, placebo	Completed, benefit on MACE*

*major adverse cardiovascular events

2.2. Data on efficacy

No new efficacy data have been provided for this referral procedure. However, data from the clinical development programme were used for evaluation of circumstances of amputation events.

All substances have demonstrated in adequately conducted pivotal clinical trials that they have shown efficacy over placebo at reducing haemoglobin A1c (HbA1c) levels when used alone and in combination with other antidiabetic medicines, as assessed during their approval procedures.

As a required pharmacovigilance activity at the time of the initial marketing authorisation, all 3 MAHs have conducted additionally long-term cardiovascular outcome studies. The studies conducted with canagliflozin (CANVAS) and dapagliflozin (DECLARE) are ongoing and final major adverse cardiovascular events (MACE) MACE results are not yet available.

For empagliflozin, the EMPA-REG trial (study 1245.25) showed a positive effect of empagliflozin treatment on death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). The results of the EMPA-REG study are further analysed and discussed in the completed procedure EMEA/H/C/002677/II/0014.

2.3. Data on safety

The MAH for canagliflozin provided mainly data from the ongoing CANVAS trial. Additionally, the clinical trial programme including 12 phase 3 and 4 studies of the global marketing dossier and studies conducted by the MAH since the marketing authorisation application was evaluated.

CANVAS is an ongoing Phase 3, double-blind, randomized, placebo-controlled, 3-arm, parallel-group, multicenter study to evaluate the effects of canagliflozin on cardiovascular (CV) outcomes in adult subjects with type 2 diabetes mellitus (T2DM). The study is fully enrolled with 4,330 randomized subjects and is scheduled to complete in the first quarter of 2017 (last patient visit). Final results for CANVAS are expected to be available second quarter of 2018. CANVAS-R (DIA4003) is an ongoing Phase 3, double-blind, randomized, placebo-controlled, 2-arm, parallel-group, multicenter study to evaluate the effects of canagliflozin on renal outcomes in adult subjects with T2DM receiving standard of care but with an inadequate glycemic control and at an elevated risk of CV events. Final results for CANVAS-R are expected to be available second quarter of 2018. CREDENCE (DNE3001), a randomized, double-blind, parallel-group, placebo-controlled, multicentre study designed to evaluate the effects of canagliflozin compared with placebo on renal and CV outcomes in subjects with T2DM and diabetic nephropathy is ongoing. Final results for CREDENCE are expected to be available in 2020.

The MAH for dapagliflozin analysed the pooled data of the development programme including 9 placebo-controlled clinical studies that included 2026 subjects receiving dapagliflozin 10 mg and 1956 subjects receiving placebo.

DECLARE, a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes, is ongoing. Final results are expected to be available in 2020.

The MAH for empagliflozin analysed the pooled data of the development programme as well as the recently completed CV outcome trial EMPA-REG (study 1245.25).

Amputation imbalances

Interim analysis of the CANVAS study (cut-off October 2015) showed an increase in the incidence of non-traumatic, lower-extremity amputations –primarily of the toe- in the canagliflozin 100 mg and 300 mg treated patients group (3.3% and 2.4%, respectively) compared to placebo (1.3%). With a mean duration of follow-up in CANVAS of approximately 4.5 years, the annualized incidence of lower-extremity amputation was 0.73, 0.54, and 0.30 events per 100 patient-year exposure in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups, respectively. Additionally, the CANVAS-R study, which has a similar patient population (i.e., with CV history or high CV risk) to the CANVAS study but with an overall shorter exposure (0.75 years), showed an annualized incidence rate of amputation of 0.70 and 0.53 events per 100 patient-year exposure to the canagliflozin group or placebo.

Subsequent interim analysis of the CANVAS trial (cut-off September 2016) showed an incidence of non-traumatic, lower-extremity amputations in the canagliflozin 100 mg and 300 mg group (3.3% and 2.6%, respectively) compared to placebo (1.3%) and incidence rates of lower-extremity amputation was 0.66, 0.52, and 0.27 events per 100 patient-year exposure in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups, respectively. For the ongoing CANVAS-R there was an incidence rate of 0.77 and 0.39 events per 100 patient-year exposure to the canagliflozin group or placebo.

No imbalances were seen in the pooled analysis of the completed phase 3 and 4 studies of canagliflozin, dapagliflozin or empagliflozin.

No imbalances in amputation events were observed within the large CV outcome trial EMPA-REG between the empagliflozin arm and the placebo arm. However, it should be noted amputations were not recorded in a structured manner.

For dapagliflozin, the DECLARE study, is on-going and so far no data on imbalances within this study have been provided. Final results are expected to be available in 2020. According to the study protocol, amputation events have so far not been captured systematically in this trial.

Treatment emergent adverse events and baseline conditions

Canagliflozin

For a comparison of the incidence, severity and development of signs and symptoms of conditions preceding surgical amputations, the MAH searched for imbalances in reporting adverse events (AEs) using selected preferred terms (PTs) from four System Organ Classes (SOCs) (Vascular disorders, Infections and infestations, Nervous system disorders, and Skin and subcutaneous tissue disorders).

This search revealed in the CANVAS overall population a higher number of events in the canagliflozin groups for skin ulcer, gangrene, wound, peripheral arterial occlusive disease, peripheral vascular disorder and intermittent claudication. However, in subjects with post-baseline amputation a higher number of reports in the canagliflozin groups compared to placebo were found with skin ulcer, gangrene, cellulitis, peripheral arterial occlusive disease and peripheral vascular disorder. It might be concluded that canagliflozin treatment elicit imbalances with regards to skin ulcer, gangrene, peripheral arterial occlusive disease, peripheral vascular disorder and intermittent claudication but events relevant for later amputation are skin ulcer, gangrene, peripheral arterial occlusive disease and peripheral vascular disorder with the most pronounced imbalance seen in skin ulcer. Neuropathic events were overall rarely reported in the subjects with amputation and seem to play either no role or a secondary role.

Overall higher incidences of adverse events in the Skin and subcutaneous tissue disorders, Vascular disorders, and Infections and infestations SOC groupings in all treatment groups were seen in the CANVAS trial compared to the analysis of pooled data of all placebo controlled non-CANVAS trials. No significant imbalances were seen in the pooled non-CANVAS studies in adverse events in the Skin and subcutaneous tissue disorders, vascular disorders, and Infections and infestations groupings.

The proportion of subjects with a history of a vascular disorder adverse event was similar across treatment groups but treatment emergent AEs (TEAEs) with regards to vascular disorders were more frequent in the canagliflozin treatment groups. Most of the subjects with vascular adverse events had no prior history of vascular adverse event. The same applies for skin/subcutaneous adverse event: a similar frequency of pre-existent skin/subcutaneous adverse events was seen in all treatment groups but a higher frequency of these adverse events in the canagliflozin groups occurring during treatment was apparent.

Although the presence of an infection/infestation adverse condition in the medical history was numerically higher in canagliflozin 100 mg and 300 mg groups (2.1% and 2.2%) relative to placebo (1.4%) as was the incidence of treatment-emergent infection/infestation adverse events (8.8%, 9.0% relative to placebo 7.0%), most patients experiencing a treatment-emergent infection/infestation adverse event while on study drug did not have a corresponding pre-existing condition.

Although the relative risk of patients with a pre-existing condition to develop a corresponding TEAE is higher in the canagliflozin group compared to the placebo group, it appears that TEAEs developed independently from the medical history. However, the MAH grouped pre-existing conditions, because single PTs were limited in number. Therefore, it is not known whether single PTs like peripheral artery occlusive disease seen to occur during treatment were already present at baseline. Overall, data support a treatment dependent development of vascular, skin and infection AEs rather than a development in consequence of a pre-existing condition.

Dapagliflozin

Frequency of adverse events occurring during treatment was similar in all treatment groups. Incidences ranged from 0.3% to 13.7%. The highest incidence of events was seen in a study of 252 patients with impaired renal function (estimated Glomerular Filtration Rate (eGFR) 30 to 59 mL/min/1.73 m2, Modification of Diet in Renal Disease (MDRD) equation) lasting 104 weeks.

In one of the larger studies of longer duration (MB102029) there were numerically more patients in the dapagliflozin group with osteomyelitis, peripheral artery occlusive disease, skin ulcer, diabetic foot and diabetic neuropathy. However, the overall numbers of events were low.

There were no differences in baseline conditions of patients experiencing amputations while receiving dapagliflozin or control. However, there is also no imbalance in amputation rate with dapagliflozin.

Within the evaluation of baseline conditions the MAH compared history of peripheral venous or artery disease (PVD/PAD) with the occurrence of vascular events during treatment in the pooled dataset of short-term and long term placebo controlled studies. These data suggest that baseline PVD/PAD do not have a major impact on the development of vascular events during treatment.

Empagliflozin

The majority of amputation events (94%) were reported in trial 1245.25 (EMPA-REG), a cardiovascular outcomes study in patients with established cardiovascular disease or at high risk for cardiovascular disease. Therefore, this study was primarily evaluated. With regard to the data on adverse events occurring under treatment in the overall population there were more patients developing peripheral arterial occlusive disease, intermittent claudication, femoral artery occlusion or osteomyelitis with empagliflozin treatment compared with placebo. However, whether these imbalances with regard to adverse events occurring during the trial are a consequence of baseline imbalances could only be evaluated for peripheral artery occlusive disease (PAOD) and diabetic foot: Patients with PAOD at baseline developed under empagliflozin treatment more vascular disorders than under placebo treatment whereas patients without PAD at baseline do not. More patients with diabetic foot at baseline than patients without diabetic foot at baseline develop diabetic foot related AEs during treatment independent of treatment.

Risk factors

Canagliflozin

The MAH evaluated the influence of baseline categorical factors on amputation risk. Baseline factors included in the evaluation were: gender, cardiovascular disease history, peripheral vascular disease history, amputation history, neuropathy history, retinopathy history, nephropathy history, any diuretic use, loop diuretic use, non-loop diuretic use, smoking, use of insulin, baseline systolic blood pressure, baseline eGFR (ml/min/1.73m2), diabetes duration (< 10 vs ≥10 yrs.), baseline HbA1c (> 8 vs ≤8%) and as baseline continuous factors age (yrs.), diabetes duration (yrs.), systolic blood pressure (mmHg), eGFR (mL/min/1.73m2), HbA1c (%) and haemoglobin (g/L). After excluding factors that proved non-significant in the univariate analyses, initial logistic regression model analysis was run. Further on, a final model for multiple regression analysis was created by removing factors that did not contribute significantly to the final model's performance.

Using this final logistic regression model stratified by treatment the following factors to be associated with an increased risk for amputation in the canagliflozin group were identified: reversible infection, skin ulcer, loop diuretics and VD AEs. Additional analyses showed an increased risk for amputation also for irreversible infection.

In the time to onset (TTO) analysis it became apparent that infection AEs were reported in close timely relationship with the amputation events, regardless of treatment, in about 46 of the 101 amputation events. Overall, there was no apparent time-relationship between the occurrence of skin AEs or vascular AEs and the time to onset of amputation. The event triggering most of the amputations, irrespective of treatment, was infection. With regard to treatment, results were inconsistent: vascular AEs were the second most reported AEs in close timely relationship with amputation events for canagliflozin 100 mg treatment but for canagliflozin 300mg treatment and placebo treatment, skin AEs were the second most reported AEs just before amputation events. Neuropathic AEs were overall rarely reported.

Subjects who experienced an amputation had numerically higher median HbA1c at baseline, irrespective of treatment. The overall time-course of HbA1c changes was similar between subjects with an amputation compared to subjects without an amputation, regardless of the treatment group. Baseline systolic blood pressure (SBP) was similar in subjects with or without an amputation as was SBP measured after randomisation and before amputation. Neither changes in HbA1c nor SBP explain the imbalance in amputation rate.

The MAH evaluated concomitant antithrombotic medications (platelet aggregation inhibitors, particularly aspirin, and other anti-thrombotic agents) as a parameter that could potentially affect peripheral vascular disease (PVD). Although fewer subjects treated with 100 mg canagliflozin had antithrombotic treatment at baseline within the subset of patients with post-baseline amputation, antithrombotic treatment was increased in the canagliflozin groups during the study period but not in the placebo group. In conclusion, the observed increase in concomitant medication in the canagliflozin groups is an indirect sign of an increase in the number of patients developing conditions to be treated with antithrombotic agents. However, it is not known whether these conditions are peripheral vascular diseases.

To further explore possible risk factors, the MAH evaluated cardiovascular disease and renal disease. In T2DM patients, both are often co-existing conditions, making it difficult to distinguish between effects caused by one or the other. Peripheral vascular disease and CV disease are known risk factors for amputations in diabetic patients. However, it appears that the amputation risk seen with canagliflozin was not further modified by the co-existence of peripheral vascular disease, CV disease nor diabetic nephropathy, or other risk factors for amputation.

At the time of the marketing authorization of canagliflozin, no imbalances in major adverse cardiovascular events (MACE) were seen between treatment groups and therefore canagliflozin may not cause amputations by worsening of these risk factors. However, no imbalance in amputation rate was seen with the available data at that time, either. As studies in patients with high risk for CV events are ongoing and final MACE results are not available, it is not possible to establish whether effects on MACE have any effect on amputations. The CANVAS trial population showed that patients with a history of vascular events are more likely to develop a vascular event during treatment with canagliflozin than during treatment with placebo. These results should, however, be interpreted with caution as the overall numbers were low. This imbalance was not seen in patients without a history of vascular events. This analysis also focused on peripheral vascular diseases. In this analysis of incidence rates of post-randomisation amputation by history of risk factors in the CANVAS population it was observed that patients without a history of vascular events suffered more often an amputation surgery during treatment with canagliflozin than during treatment with placebo (incidence difference 0.51). This difference was larger in patients without a PVD history than in patients with PVD history (incidence difference 0.29). It might be therefore concluded that patients with PVD history are more likely to develop peripheral vascular events when treated with canagliflozin compared to placebo but this does not translate into higher amputation rates. These results should, however, be interpreted with caution as sample sizes of the subgroups evaluated differed much and results are associated with a high variability of the derived point estimates.

Among the completed studies in the Canagliflozin Phase 3 and 4 development program, results provided for study 3004 (subjects with T2DM having moderate renal impairment) are remarkable, even though this study was neither the longest nor the largest clinical trial: although overall the probability of detecting imbalances increases with sample size and study duration, the majority of amputation events were seen in study 3004. The overall (canagliflozin + placebo) incidence rate of amputation in study 3004 was 1.7 events per 100 patient years (1 event on 100mg, 1 event on 300mg and 2 events

on placebo). This study also accounts for the highest percentage of all assessed adverse events compared to the other trials. Study 3004 included patients who have moderate renal impairment. If this patient population is population at risk, a higher amputation rate should be seen in other studies with renally impaired patients. CREDENCE an ongoing trial that includes diabetic patients with stage 2 or 3 chronic kidney disease and macro-albuminuria, will report results in 2020. In the linear regression model evaluating risk factors, reduced baseline eGFR did however not show a significant association. The MAH evaluated the study populations included in CANVAS, CANVAS-R and CREDENCE for baseline characteristics predictive for amputations. Amputation history, neuropathy and loop diuretic use were more common in patients in CREDENCE trial compared to patients in CANVAS and CANVAS-R. Further analysis confirmed that renal impairment is a risk factor for amputations. However, an increased risk for patients treated with canagliflozin could not be derived from the data provided so far as study 3004 is too small and the CREDENCE trial is still blinded.

The MAH stated that there were differences between treatments in the baseline and post-baseline use of antidiabetic agents in the CANVAS study, mainly with regards to biguanide and sulphonylurea use. However, it is unclear whether this finding plays a significant role in explaining the imbalance between treatments regarding amputations.

Dapagliflozin

Due to the overall small number of amputation events and the lack of an amputation imbalance in the clinical trials completed so far, it was difficult to evaluate risk factors in patients with amputation.

With regard to baseline conditions there were no differences in patients experiencing amputations while receiving dapagliflozin or control.

Marked abnormalities of haematocrit (>55%) and haemoglobin (>18 g/dL) were more common in patients treated with dapagliflozin compared to placebo. Increases of haematocrit or haemoglobin did not have an impact on the risk of amputations.

Cardiovascular and renal diseases are well-known risk factors for amputation regardless of treatment. All subjects with amputations were renally impaired at baseline. However, the majority of patients in the dapagliflozin group had chronic kidney disease (CKD) stage 2 whereas in the placebo group most patients had CKD stage 1 and nine of the 15 patients with amputations came from two larger cardiovascular studies.

Empagliflozin

To identify whether specific subgroups of patients could be at increased risk of amputations, baseline conditions and concomitant medications were assessed. The baseline conditions considered were: gender; age (categorical analysis, <65 years vs. ≥65 years); race; geographical region; body mass index (categorical analysis, <30 kg/m2 vs. ≥30 kg/m2); time since type 2 diabetes mellitus diagnosis (categorical analysis, ≤5 years, >5 to 10 years, >10 years); baseline HbA1c (categorical analysis, <8.0% vs. ≥8.0%); baseline estimated glomerular filtration rate (categorical analysis according to KDIGO CKD stages; blood pressure control; concomitant use of diuretics and loop diuretics; concomitant use of antidiabetic drugs (metformin, sulfonylurea, and insulin); established cardiovascular diseases; diabetic retino-, neuro-, and nephropathy; and diabetic foot.

The analyses revealed that female patients treated with empagliflozin had a higher frequency of LLA compared to placebo (all empagliflozin 22 patients [1.6%] vs. placebo 5 patients [0.8%]). However, this finding was not seen in any other evaluation.

An increased incidence of amputation events with regard to baseline conditions but independent of treatment was seen in patients with:

Cardiovascular disease

- Peripheral artery occlusive disease (PAOD): Amputation frequency was 6.3% for placebo and 5.5% for all empagliflozin in subjects with PAOD compared to 0.7% for placebo and 0.9% for all empagliflozin in subjects without PAOD.
- Diabetic foot: Amputation frequency was 15.9% for placebo and 14.4% for all empagliflozin in subjects with diabetic foot compared to 0.9% on placebo 1.1% for all empagliflozin in subjects without diabetic foot.
- History of Coronary artery bypass grafting (CABG): amputation frequency was 2.5% for placebo and 2.3% for all empagliflozin in subjects with CABG compared to 1.6% for placebo and 1.7% for all empagliflozin in subjects without CABG.

Renal disease

- LLA was reported more frequently in patients with moderate or severe renal impairment than in patients with normal or mildly impaired renal function

Use of diuretics

- A small increase in the frequency of LLA was seen in patients who used diuretics and loop diuretics. A similar increase was seen in the events potentially leading to LLA.

Use of antidiabetic medication

- Patients treated with insulin had a higher frequency of LLA.

Patients with a history of stroke, coronary artery disease and hypertension did not have a higher frequency of LLA.

Patients treated with metformin had even a lower frequency of LLA compared to patients not treated with metformin. A similar result was seen with the use of sulfonylurea.

There was no difference in the mean and median change from baseline values of haematocrit neither at the end of the treatment, nor in the maximal change from baseline value on treatment in either the placebo or empagliflozin arms for patients with LLA compared to the patients without such an event. The mean and median change from baseline maximal and last values on treatment of haematocrit (HCT) did not differ between the patients with and without PAOD or diabetic foot related AEs, two conditions which lead to LLA, neither in the placebo nor in empagliflozin treatment arms.

Possible Mechanism of action - Volume depletion

Canagliflozin

The MAH favoured as possible mechanism for the amputation findings the hypothesis that osmotic diuresis and concomitant reduction in extravascular volume lead to altered tissue perfusion. If volume depletion is the main trigger for amputation risk a dose response relationship would be expected, which is currently not observed. It was also considered that malnutrition of the lower limb is more likely due to a long-term volume reduction rather than a short-term volume depletion leading to clinically noticed volume depletion events. However, although volume depletion events occurred mainly in the first three months after treatment start, amputation events have been reported throughout the whole observational period.

Reduced glucose supply to peripheral tissues accompanying glycosuria and volume reduction may also play a role in volume depletion. Osmotic diuresis should occur to a lesser extent in renally impaired patients. Although patients in the CANVAS and CANVAS-R study are expected to be a population with compromised vascular function, who is therefore at particularly high overall risk for amputations, the highest overall incidence of amputations in the completed studies in the Canagliflozin Phase 3 and 4 development program were observed in study 3004 which included renally impaired patients. Renally impaired patients therefore appear to be at even higher risk for amputations. Currently a clinical trial (CREDENCE) is ongoing in renally impaired patients with final results expected in 2020

Dapagliflozin

As no difference in amputation risk has been found with dapagliflozin it is difficult to evaluate the mechanism for amputation imbalance. Volume depletion is reported slightly more often in subjects treated with dapagliflozin compared with subjects treated with placebo. The difference between treatment groups was also seen in subjects older than 65 years of age, on loop diuretics, and with renal impairment. However, all subgroup results are based on very few events.

Empagliflozin

In EMPA-REG, 5 patients with LLA also had AEs related to volume depletion. The frequency of volume depletion related AEs was not significantly increased in patients with LLA. It appears that although there was a slightly higher number of volume depletion AEs in the empagliflozin 25 mg group than in the placebo group, there was no relation between patients with LLA and patients reporting volume depletion AEs. It also appeared that empagliflozin has an effect on LLA if patients use (loop) diuretics but not if patients do not use (loop) diuretics. However, the low number of the subgroup of patients with LLA does not allow for a definite conclusion.

SGLT2/SGLT1 affinity - off-target activity

Canagliflozin

Regarding mechanisms by which canagliflozin may increase the risk of amputations, the MAH considered that a direct or indirect influence of SGLT inhibition on factors predisposing or leading to amputation was unlikely. This is justified by the fact that SGLT2 is not known to be expressed in vascular, neural, non-renal tubule epithelial, mesenchymal or hematopoietic cells. However, further evaluation of SGLT1/2 affinity has shown that canagliflozin is selective for SGLT2, but with a small remaining affinity to SGLT1 that is higher for canagliflozin than for other members of the class. Canagliflozin has been shown to act similarly to dapagliflozin with regards to urinary glucose excretion (UGE) in the first four hours but showed a higher excretion beyond the fourth hour. Whether this is due to higher overall potency of the drug, prolonged elimination with partly reabsorption of canagliflozin in the proximal tubules or additional SGLT1 binding in the kidney is unknown. For Canagliflozin 300 mg, it has been shown that the substance can have a clinical effect on SGLT1 in the lumen of the intestine in the form of reducing glucose absorption. The MAH considers plasma concentration of the free (unbound to plasma proteins) and non-metabolised drug to be too low to produce a clinical effect with regard to amputation. However, if the drug acts from the luminal side of the proximal tubules of the kidney or the intestine, low plasma concentration and high protein binding might not be crucial factors. SGLT1 has also been found in the endothelium of cerebral, renal, and mesenteric arteries. It has been connected with cardiac reorganization after ischemic insult and wound healing from heat injury. The clinical relevance of these findings is unknown (Turk, 1991).

Dapagliflozin

Dapagliflozin shows a high selectivity for SGLT2. According to the dapagliflozin MAH, the increased glycosuria seen with canagliflozin compared to dapagliflozin is attributed to the fact that SGLT1 inhibition further reduces kidney glucose reabsorption. The dapagliflozin MAH considers that SGLT1 inhibition may be involved in the occurrence of amputation events and is a potential explanation for certain differences in the safety profiles between canagliflozin on one hand and dapagliflozin/empagliflozin on the other hand. However, all three SGLT2i are selective for SGLT2 with a remaining very small SGLT1 inhibition, which extent varies between the different substances. SGLT1 has been found in tissues other than kidney or the intestine but there are no studies evaluating SGLT1 in the endothelium of the lower limb. An action on SGLT1 in these tissues is possible but not yet confirmed. SGLT1 action in the kidneys is possible but also yet not established.

Empagliflozin

Empagliflozin demonstrated the highest selectivity towards SGLT2 in the class. In humans, empagliflozin has a high specificity for SGLT-2 vs SGLT-1 (selectivity ~5000x) compared to dapagliflozin (selectivity ~1200x) and canagliflozin (selectivity ~158x). It is unlikely that inhibition of SGLT-1 will be achieved at clinical therapeutic exposures of empagliflozin. The rat is considered as the non-clinical species, in which at high doses there is the highest inhibition of SGLT-1 due to the lower specificity towards SGLT-2. In rat, there is no evidence for an effect of empagliflozin on microvasculature in non-clinical toxicity studies. Although publications suggest that SGLT1 is present in tissues other than the kidney or the intestine and although publications suggest that SGLT1 may be involved in recovery from cellular injury or may have an impact on muscle glucose metabolism, literature concludes there is no direct link between SGLT-1 inhibition and an increased risk of amputations. However, as data is limited, a SGLT1 involvement cannot be excluded (Banerjee, 2009; Elfeber, 2004 (2); Gaudreault, 2006; Ikari, 2004; Kanwal, 2016; Kolka, 2005; Vemula, 2009).

Class effect

A meaningful inhibition of SGLT1 or other members of the transporter family may be doubted due to the high selectivity for SGLT2 and because the systemic exposure of the free drug (unbound to plasma proteins) may be too low to induce relevant inhibition. However, as all SGLT2 inhibitors follow the same general mode of action, differences in selectivity for different members of the SGLT family or different potencies in inhibiting the transporter would be one explanation for differences seen in amputation rate with SGLT2 inhibitors. In addition, if canagliflozin acts from the luminal side of the renal tubules or the intestine then low systemic exposure as well as high protein binding is no argument against transporter inhibition. The MAH of canagliflozin suggested that the most likely mechanism is increased urinary glucose excretion due to SGLT2 inhibition leading to volume reduction and impaired tissue perfusion in the lower limb so that patients with already impaired tissue perfusion will more likely develop conditions that lead to amputations. This mechanism, however, would be a class effect. After review of the available information, a class effect can neither be proven nor disproven. On one hand, even if differences in potency, selectivity and pharmacokinetics may lead to differences in the risk profile, as all members of the class follow the same mode of action, in principle they should share similar risks. On the other hand, it should be considered that an increased risk of amputations was observed for canagliflozin in an interim-analysis of two ongoing (blinded) trials, but no imbalances in amputation events were observed in analyses of other completed trials of canagliflozin, dapagliflozin and empagliflozin and data for dapagliflozin from the large CV study (DECLARE) are not yet available. It should also be taken into account that data on amputations was not systematically collected; hence misclassification of amputation events might bias the results of

these analyses. The magnitude and direction of this bias is therefore unknown. Notably, subgroups of patients at increased risk for amputations could not be clearly identified in the analyses of the conditions that are risk factors for surgical amputations.

Given the data provided and discussed to date it is considered that "Lower limb amputations" is an identified risk for canagliflozin. In addition, due to remaining uncertainties in the analysis of the available data as a result of possible misclassification of the outcome (amputations), "Lower limb amputations" is a potential risk for dapagliflozin and empagliflozin-containing products. The relevant data should be collected in future trials with SGLT2-containing products, as well as from the post-marketing setting and discussed in future PSURs until sufficient data becomes available to either confirm or refute the risk of amputations for SGLT2 inhibitors in general or canagliflozin, dapagliflozin and/or empagliflozin in particular. Communication of this risk via product information and additional pharmacovigilance activities to be reflected in the RMP is considered warranted.

3. Benefit-risk balance

Benefits

From an efficacy perspective, data from the clinical development programme assessed during the marketing authorisation procedure of canagliflozin, dapagliflozin and empagliflozin containing medicinal products have shown that sodium-glucose co-transporter 2 (SGLT2) inhibitors used together with diet and exercise, either alone or in combination with other diabetes medicines, are effective medicines in patients with type 2 diabetes with regard to their ability to improve glycaemic control.

No new efficacy data have been assessed during this referral procedure.

Uncertainty about benefits

Large clinical studies for canagliflozin (CANVAS, CANVAS-R and CREDENCE) and dapagliflozin (DECLARE) are ongoing and final MACE results are not yet available. Data is missing for canagliflozin regarding use in paediatric patients, use in pregnancy and by nursing mothers, use in very elderly patients (≥ 85 years), patients with severe hepatic impairment and patients with congestive heart failure defined as New-York Heart association (NYHA) class III-IV. There is data missing regarding the use in patients with severe renal impairment (eGFR<30mG/min/1.73m2).

For dapagliflozin, there is limited data for the use in patients who are non-white and/or older than 65 years old.

Data is missing for empagliflozin regarding paediatric use as well as, for use in elderly patients, pregnancy/breast-feeding, and for use in patients with severe hepatic impairment.

Risks

Identified risks for canagliflozin as outlined in the risk management plan are vulvovaginal candidiasis, balanitis or balanoposthitis, urinary tract infections, hypoglycemia in combination with insulin or glucose-independent insulin secretagogues, volume depletion, bone fractures, renal impairment/renal failure, hypersensitivity and diabetic ketoacidosis with atypical presentation.

Identified risks for dapagliflozin as outlined in the risk management plan are genital infections, urinary tract infections and diabetic ketoacidosis with atypical presentation.

Identified risks for empagliflozin as outlined in the risk management plan are urinary tract infection, genital infection, volume depletion hypoglycemia (with insulin and/or sulphonylurea) and diabetic ketoacidosis with atypical presentation.

An updated interim analysis of amputation events the CANVAS trial (cut-off September 2016) provided during the procedure showed an incidence of non-traumatic, lower-extremity amputations in the canagliflozin 100 mg and 300 mg group (3.3% and 2.6%, respectively) compared to placebo (1.3%) and incidence rates of lower-extremity amputation was 0.66, 0.52, and 0.27 events per 100 patient-year exposure in the canagliflozin 100 mg, canagliflozin 300 mg, and placebo groups, respectively. For the ongoing CANVAS-R there was an incidence rate of 0.77 and 0.39 events per 100 patient-year exposure to the canagliflozin group or placebo.

No imbalances in amputation events were observed within the large CV outcome trials evaluating empagliflozin (EMPA-REG) or dapagliflozin (DECLARE), but amputation events were not systematically captured within these trials. Final results for the DECLARE study are expected to be available in 2020.

Similarly, no imbalances were seen in the pooled analyses of the completed phase 3 or 4 of canagliflozin, dapagliflozin or empagliflozin.

Uncertainties about risks

Potential risks for canagliflozin include clinical consequences of increased haematocrit, photosensitivity, hypoglycaemia in the absence of insulin or glucose-independent insulin secretagogues, off-label use for weight loss and pancreatitis.

Potential risks for dapagliflozin include hypoglycaemia, volume depletion, clinical consequences of increased haematocrit, renal impairment/failure, bone fracture, liver injury, hypersensitivity reactions, bladder cancer, breast cancer, prostate cancer and off-label use of dapagliflozin in specific populations.

Potential risks for empagliflozin include urinary tract carcinogenicity, liver injury, off-label use (e.g. for weight loss in non-T2DM patients) and bone fracture.

With regard to amputation risk neither the mechanism behind the occurrence of amputation events in canagliflozin treated patients in large clinical trials nor the risk factors beyond common risk factors for amputation events in diabetic patients are known. Final results for the CANVAS and CANVAS-R studies are expected to be available in 2018. Final results for the DECLARE study are expected to be available in 2020. Currently, a class effect can neither be confirmed nor refuted.

Conclusion

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 above 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.

4. Risk management

4.1. Safety specification

The PRAC considered that lower limb amputation should be included as important risk in the risk management plan (RMP) for all SGLT2 inhibitors. PRAC concluded that lower limb amputation should be considered an important identified risk for canagliflozin and an important potential risk for dapagliflozin and empagliflozin in the respective RMPs. The MAH(s) have amended their respective RMPs(s) accordingly.

4.2. Pharmacovigilance plan

PRAC requested that the MAHs also implement the following pharmacovigilance measures (routine and additional pharmacovigilance activities):

4.2.1. Routine pharmacovigilance: Specific adverse reaction follow-up questionnaires

- All MAHs should capture amputation cases “adverse event of special interest” in all ongoing and future clinical studies of duration superior to 12 weeks for all SGLT2 inhibitors as well as preceding events, including for cases not leading to an amputation event, as per a list of preferred terms provided in attachment 2 and to be specified in the RMP and included in the safety specification;
- All MAHs should implement a dedicated case report form (CRF) for clinical trials and targeted follow-up questionnaires for post-marketing reports in order to capture and better characterise amputation events as well as relevant events preceding amputation. Use of the case report forms (CRFs) and questionnaires should be triggered by the reporting of events as per the list of preferred terms specified in the RMP; apart from searching amputation events, MAHs should search for events preceding an amputation. The reporting of any of these events should act as a trigger for the dedicated CRF or targeted follow-up questionnaire. The report forms (CRF (clinical trials) and questionnaire (post-marketing reports)) should be kept as short as possible, in order to not impose too much burden on clinical practice while still collecting the relevant information. Relevant

information should include details regarding amputation (level/date), aetiology leading to amputation/preceding events (start date, management, complications), exposure to the drug (start date, end date, dosage) and medical history. Questions about preceding events should at least include peripheral vascular disease, diabetic foot, peripheral neuropathy, lower limb infection including ulcer and gangrene and dehydration. Relevant medical history should at least include diabetes type, renal impairment estimated Glomerular Filtration Rate (eGFR)), tobacco use and level of diabetes control (HbA1c).

- As a result, RMP updates for all products should be submitted within 1 month after EC decision on this procedure taking into account the above requests.

4.2.2. Additional pharmacovigilance activities

- The MAH for canagliflozin proposed an observational study in a US database as a category 3 study in the RMP as well as relevant timelines for protocol and results submissions. The MAH also included the feasibility assessment for an EU observational study for evaluation of amputations in EU databases as a category 3 PASS. The study protocol and feasibility assessment for these 2 studies as well as the timelines for submission of the results of the US observational study should be submitted for assessment no later than one month following the European Commission decision on this referral procedure;
- The MAH for canagliflozin has also proposed the conduct of a meta-analysis as a category 3 study in the RMP. The PRAC considers that the analysis of the meta-analysis should include, for each study (including CREDENCE, CANVAS and CANVAS-R), a graph of the cumulative incidence of amputation events and in addition, relevant preceding adverse events of special interest (gangrene, osteomyelitis, etc.) over time. This analysis should also provide the cumulative proportion of patients with amputations and additionally relevant preceding events and show the number of patients "at risk" at relevant time points. The protocol of this meta-analysis should be submitted earlier for review than initially proposed. Timelines for submission of the meta-analysis protocol that will allow for sufficient time for regulatory review of the protocol should be included in the updated RMP, that should be submitted no later than one month following the European Commission decision on this procedure ;
- The MAH for dapagliflozin has proposed the conduct of a meta-analysis as a category 3 PASS in the RMP. The PRAC considers that this analysis, should include, for each study (including DECLARE, D1690C00018 and D1690C00019), a graph of the cumulative incidence of amputation events and in addition, relevant preceding adverse events of special interest (gangrene, osteomyelitis, etc.) over time. This analysis should also provide the cumulative proportion of patients with amputations and additionally relevant preceding events and show the number of patients "at risk" at relevant time points. Timelines for submission of the protocol of this meta-analysis for review should be included in the updated RMP that should be submitted within 1 month after European Commission decision on this procedure. .
- The MAH for empagliflozin has proposed the conduct of a meta-analysis of the two chronic heart failure (HF) studies together with the EMPA-REG trial (1245.110, 1245.121, and 1245.25) as a category 3 PASS in the RMP as well as relevant timelines for protocol and results submissions. The PRAC considers that the analysis of the meta-analysis should include, for each study, a graph of the cumulative incidence of amputation events and in addition, relevant preceding adverse events of special interest (gangrene, osteomyelitis, etc.) over time. This analysis should also provide the cumulative proportion of patients with amputations and additionally relevant preceding events and show the number of patients "at risk" at relevant time points. The MAH should also consider

analysing the two studies in the HF population, namely 1245.110, 1245.121, separately as well as conducing separate analyses of patients with and without T2DM. Timelines for submission of the protocol of this meta-analysis for review should be submitted within the updated RMP to be submitted within 1 month after European Commission decision on this procedure.

4.2.3. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information were necessary in order to minimise the risk of lower limb amputation associated with the use of SGLT2 inhibitors. These changes include amendments to section 4.4 (for canagliflozin, dapagliflozin and empagliflozin) and 4.8 (for canagliflozin only) of the SmPC as presented in Attachment 1.

The Package Leaflet was amended accordingly.

5. Grounds for Recommendation

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for the products listed in Annex A of the PRAC recommendation;
- 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.

Attachment 1 - Amendments to the product information as recommended by the PRAC

For all products in Annex I, the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below

Summary of product characteristics

Canagliflozin

4.4 Special warnings and precautions for use

A warning should be added as follows:

Lower Limb Amputations

In ongoing, long-term clinical studies of canagliflozin in T2DM patients with cardiovascular disease (CVD) or at high risk for CVD, an increase in cases of lower limb amputation (primarily of the toe) has been observed in patients treated with canagliflozin.

As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown. However, as precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with canagliflozin in patients that develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

4.8 Undesirable effects

The following adverse reaction(s) should be added under the SOC Surgical and medical procedures with a frequency uncommon as follows:

4.8 Undesirable effects

System organ class Frequency	Adverse reaction
Surgical and medical procedures	
uncommon	lower limb amputations (mainly of the toe) especially in patients at high risk for heart disease

Package leaflet

Section 2: What you need to know before you take canagliflozin

Warnings and precautions

It is important to check your feet regularly and adhere to any other advice regarding foot care and adequate hydration given by your health care professional. You should notify your doctor immediately if you notice any wounds or discolouration, or if your experience any tenderness or pain in your feet. Some studies indicate that taking canagliflozin may have contributed to the risk of lower limb amputation (mainly toe amputations).

Section 4: Possible side effects

Other side effects:

Uncommon (may affect up to 1 in 100 people)

- lower limb amputations (mainly of the toe) especially if you are at high risk of heart disease

Dapagliflozin

4.4 Special warnings and precautions for use

A warning should be added as follows:

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

Package leaflet

Section 2: What you need to know before you take dapagliflozin

Warnings and precautions

Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

Empagliflozin

4.4 Special warnings and precautions for use

A warning should be added as follows:

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

Package leaflet

Section 2: What you need to know before you take dapagliflozin

Warnings and precautions

Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

Attachment 2 - List of PTs for preceding events

Vascular AEs

Angiopathy
Arterial bypass operation
Arterial disorder
Arterial graft
Arterial occlusive disease
Arterial stenosis
Arterial stent insertion
Arteriosclerosis
Arterial thrombosis
Arterial therapeutic procedure
Diabetic microangiopathy
Diabetic vascular disorder
Femoral artery occlusion
Iliac artery occlusion
Intermittent claudication
Ischaemic limb pain
Microangiopathy
PAOD Peripheral arterial occlusive disease
Peripheral ischaemia
Peripheral coldness
Peripheral artery stenosis
Peripheral artery restenosis
Peripheral artery occlusion
Peripheral artery thrombosis
Peripheral vascular disorder
Peripheral ischaemia
Peripheral arterial re-occlusion
Peripheral vascular disorder
Poor peripheral circulation
Peripheral artery angioplasty
Peripheral endarterectomy
Peripheral artery bypass
Peripheral artery stent insertion
Spontaneous amputation
Thrombosis

Diabetic foot related AEs

Atherosclerotic gangrene
Bone abscess
Diabetic foot
Diabetic foot infection
Diabetic gangrene
Diabetic neuropathic ulcer
Diabetic ulcer
Dry gangrene
Cellulitis enterococcal

Cellulitis staphylococcal
Cellulitis streptococcal
Cellulitis gangrenous
Extremity necrosis
Gangrene
Infections Cellulitis
Infected skin ulcer
Infected skin ulcer
Ischaemic ulcer
Localised infection
Necrosis ischaemic
Neuropathic ulcer
Osteitis
Osteomyelitis
Osteomyelitis acute
Osteomyelitis bacterial
Osteomyelitis chronic
Osteomyelitis fungal
Osteomyelitis salmonella
Osteonecrosis
Penetrating atherosclerotic ulcer
Post-operative wound infection
Skin erosion
Skin ulcer
Staphylococcal osteomyelitis
Soft tissue infection
Subperiosteal abscess

Wound / Infection

Abscess limb
Burn infection
Impaired healing
Wound
Skin wound
Skin infection
Subcutaneous abscess
Vasculitic ulcer
Wound abscess
Wound complication
Wound dehiscence
Wound infection
Wound infection bacterial
Wound infection fungal
Wound infection staphylococcal
Wound infection pseudomonas
Wound necrosis
Wound sepsis
Wound treatment

Nervous System Disorders

Areflexia
Autonomic neuropathy
Burning sensation
Diabetic neuropathy
Hypoaesthesia
Neuropathy peripheral
Paraesthesia
Peripheral sensory neuropathy
Peripheral sensorimotor neuropathy
Sensory disturbance

Volume depletion

Hypovolaemia
Dehydration

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