21 April 2016
EMA/PRAC/271175/2016

PRAC List of questions

To be addressed by the marketing authorisation holder(s)

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

Procedure number: EMEA/H/A-20/1442

INVOKANA (canagliflozin)

VOKANAMET (canagliflozin / metformin)

INN/active substance: Canagliflozin

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The MAH is requested to provide responses to the following questions:

Please note that PRAC is not asking for unblinding of data that would compromise the integrity of the on-going trial. Data from on-going trials should only be provided, when possible, with agreement of the responsible IDMCs.

Amputation events and preliminary stages

1. The MAH is requested to provide an overview of cases of amputations in the canagliflozin group and the placebo groups within CANVAS and CANVAS-R. In this overview, the MAH should discuss conditions preceding surgical amputations, compliance with foot care recommendations and should comment on possible centre effects within the trials.

2. Data on events of amputation, skin ulceration, peripheral ischemia, peripheral vascular disease, 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 by submitting data on the event numbers and overall numbers of patients in active and comparison groups 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

3. Provide, as available, complete results of analyses evaluating possible risk factors.

   Please additionally present separate analyses for risk factors for canagliflozin 100 mg and canagliflozin 300mg (ie present all analyses relating to risk factors not only for the overall group of canagliflozin patients but also for the single treatment groups 100mg and 300mg).

4. The MAH is requested to discuss possible mechanisms by which canagliflozin may increase the risk of amputations including data on volume depletion, concomitant antidiabetic medication and other possible mechanisms than volume depletion.

Time to event analysis

5. The MAH should provide further clarification on handling of censoring in the time-to-event analysis on first post-randomization amputation.

Data collection

6. The MAH should state how amputations were captured as adverse events in any of the trials performed with canagliflozin and if information was collected in various databases.

CREDENCE trial

7. Please comment on the rate of amputations observed and related events within the different treatment groups of the ongoing CREDENCE trial (Evaluation of the Effects of canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy, NCT02065791) as far as available.

Pharmacovigilance Activities

8. Please discuss possibilities to further explore the risk of amputations throughout additional pharmacovigilance measures. Please discuss possibilities for meta-analysis and meta-regression of clinical trials performed with canagliflozin.

9. Please also discuss the feasibility for conducting observational studies to address this potential risk including addressing the availability of European Data.

Risk minimisation

10. Based on the evaluation of the potential amputation risk in response to the questions above, the MAH is requested to propose appropriate risk minimization measures as necessary, including changes to the SmPC/PL, and additional risk minimisation activities, to mitigate the risk of amputations, if confirmed.