11 June 2015
EMA/PRAC/390892/2015

PRAC List of questions

To be addressed by the marketing authorisation holders

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

SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)

Invokana EMEA/H/A-20/1419/C/2649/0011

Vokanamet EMEA/H/A-20/1419/C/2656/0007

Forxiga EMEA/H/A-20/1419/C/2322/0021

XigDuo EMEA/H/A-20/1419/C/2672/0012

Jardiance EMEA/H/A-20/1419/C/2677/0007

Synjardy EMEA/H/A-20/1419/C/3770/0001

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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. Diabetic ketoacidosis (DKA) is a serious, often life-threatening condition. It is a subset of ketoacidosis or ketosis in diabetic patients and a type of acidosis that usually develops when insulin levels are too low. A safety warning on DKA was recently issued by the FDA for this therapeutic class. A search in Eudravigilance (EV) database was performed by the EMA for the SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin (PTs: ketoacidosis, diabetic ketoacidosis, ketosis). Several cases of DKA were identified in EV in diabetic patients for the three active substances with a suggestive causal association. Taking into account the severity of these cases and the general pattern seen across these medicinal products further investigation is required.

The marketing authorisation holders (MAHs) are requested to submit relevant data that are already submitted to other regulatory authorities and to also address the following questions:

Question 1

a. The MAHs should provide a cumulative review and discussion of all events of diabetic ketoacidosis (DKA) (typical or atypical presentation) in association with their SGLT2 inhibitor product in clinical trials, literature and post-marketing. In the requested cumulative review the special focus should be on ketone, glucose and lactate levels, time to onset, dose including dose relationship, severity, predisposing factors, indication of the SGLT2 inhibitor (type 1 or type 2 diabetes), outcome and how the diagnosis of DKA was confirmed. The following MedDRA PTs should be included: Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Ketoacidosis, Ketonuria, Ketosis, Urine ketone body present, Acidosis, Metabolic acidosis, Blood ketone body present, Blood ketone body increased. Line listing of cases and CIOMS forms should be annexed to the cumulative review.

b. The MAHs are requested to provide a table summarising all information on cases from spontaneous and solicited sources providing the following information per case.

- PTs reported including outcome (hospitalisation, ICU, fatal, etc.)
- Age, Gender
- Type 1 or type 2 diabetes
- Concomitant conditions e.g. infection, surgery, dehydration, weight loss before event, low caloric diet before event;
- Concomitant medication comprising insulin or antidiabetic secretagogue medication (yes or no) including any dose change (specify dose change if yes and include time to event from dose change);
- Change in SGLT2 inhibitor dose before event (specify dose change if yes and include time to onset of event from dose change);
- Laboratory values: Information on lactate, blood/urine ketones, arterial/venous ph, blood/urine glucose and any other lab values available (specify values if yes including information on whether abnormal values reported or not); information on endogenous insulin production at the time of event (i.e. C-peptide if available) and how diagnosis of ketoacidosis was confirmed.
- other signs and symptoms before diagnosis

Question 2

The MAHs are requested to provide a review and discussion of cases of ketonaemia and ketonuria and other events associated with the MedDRA PTs cited above observed within clinical trials in all indications with their medicinal products containing SGLT2 inhibitors compared to placebo or other comparators and to discuss the potential influence of risk factors for the development of ketoacidosis. Comments on time-course observed should be provided. The MAHs should provide a table indicating the percentage of the above mentioned events for each clinical trial for the SGLT2 inhibitors as well as the comparison groups (indicating number of events and number of patients under treatment, e.g. frequency table of events and incidence density rate).

Question 3

The MAHs should evaluate the potential mechanisms by which SGLT2 inhibitors could induce DKA. This evaluation should include, but not be restricted to, a discussion of the following issues:

a. In some of the cases (e.g. with canagliflozin), the diabetic ketoacidosis developed shortly after the discontinuation of treatment, but continued glucosuria was observed. The MAH should discuss whether a prolonged SGLT2 inhibition has been observed after continuous treatment.

b. Insulin secretion is usually stimulated by increasing ketone levels. In some of the cases it would be expected that the patients had an endogenous insulin secretion which should have been stimulated by ketosis. The MAHs should provide data and discuss whether any inhibitory effect of SGLT2 inhibitors on insulin secretion has been observed in the pre-clinical or clinical data.

c. Ketoacidosis is enhanced by an increased glucagon/insulin ratio. The MAHs should provide data including any publications on the effect of the products on the glucagon/insulin ratio.

d. The MAHs should perform a literature review of the safety issue and discuss the outcome. An initial publication list (but not restrictive) is given below.

Question 4

The MAHs should discuss any mechanistic and preclinical studies performed that could be of relevance to this safety issue. They also should discuss the possibilities for further studies on the potential mechanism of these events.

Question 5

Taking into account the evidence from all relevant data sources, the MAHs are requested to discuss patient exposure, frequency, severity and outcomes of DKA events in patients using their SGLT2 inhibitors medicinal products compared to the type 2 diabetes population background rates of DKA as well as to background rates in type 1 diabetes patients.

Question 6

The MAHs should evaluate the risk factors as well as populations at risk within all the patient populations using SGLT2 inhibitors.

Question 7

The MAHs should discuss the need for additional pharmacovigilance measures and the possibility for respective joint actions by all MAHs of SGLT2 inhibitors for collecting information on

a. risk factors and patient population at risk for DKA;

b. the use in non-approved indication of type 1 diabetes mellitus (T1DM) ('off label').

Question 8

The MAH is requested to discuss the impact of the results of occurrence of DKA on the benefit–risk balance of their product in the authorised indication and consider how the benefit-risk balance may differ in patient populations.

Question 9

Based on their evaluation of the benefit – risk balance of their product, the MAHs should provide proposals and rationale for any risk minimisation measures (including changes to the product information) regarding the occurrence of DKA with atypical presentation, the patient populations at risk, the use in non-approved indications ('off label') and actions to prevent this event, as well as proposals on how their effectiveness should be monitored.

Question 10

The MAHs should discuss necessary updates of their risk management plans (RMPs).

References:

1. Tomohide H, Yoshiro K, Hideki K, Masaki K,Ena N, Yukako S, Chika K,Sami S,Yuichiro Y, Rina K, Toshihito A,Saeko N, Hiromi N, Eriko T,Emi A,Mikio M, Atsuko W, Koichi K, Jiro N. Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Invest 2015 doi: 10.1111/jdi.12330
2. Hine J, Paterson H, Abrol E, Russell-Jones D, Herring R. SGLT inhibition and euglycaemic diabetic ketoacidosis. Lancet Diabetes Endocrinol. 2015 May 26. pii: S2213-8587(15)00204-1.
3. Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thévenet J, Beaucamps C, Delalleau N, Popescu I, Malaisse WJ, Sener A, Deprez B, Abderrahmani A, Staels B, Pattou F. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med. 2015 May;21(5):512-7
4. Ekpeberg C, Longo-Mbenza B, Blanco-Blanco E. Islet immunity and beta cell reserve of indigenous black South Africans with ketoacidosis at initial diagnosis of diabetes. Ethn Dis 2013;23:196–201.
5. Umplerrez GD, Smiley D, Kitabachi AE. Narrative review: Ketosis-prone type 2 diabetes mellitus. Ann Internal Med 2006;144:350–57.
6. Seok H, Jung CH, Kim SW, et al. Clinical characteristics and insulin independence of Koreans with new-onset type 2 diabetes presenting with diabetic ketoacidosis. Diabetes Metab Res Rev 2013;29:507–13.