18 February 2016
EMA/PRAC/50218/2016
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

SGLT 2 inhibitors

Procedure numbers:

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

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

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

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

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

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

Note

Assessment report as adopted by the PRAC and taken into account by the CHMP in its opinion with all information of a commercially confidential nature deleted.

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List of abbreviations

A	Acidosis
AE	Adverse event
AHA	Antihyperglycemic agent
BKBI	Blood ketone body increased
BKBP	Blood ketone body present
CI	Confidence interval
DHC	Diabetic ketoacidotic hyperglycemic coma
DHPC	Direct healthcare professional communication
DKA	Diabetic ketoacidosis
DLP	Data lock point
DM	Diabetes mellitus
DPP-4i	Dipeptidyl peptidase-4 inhibitors
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EV	Eudravigilance
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-1
KA	Ketoacidosis
K	Ketosis
KU	Ketonuria
LADA	Latent autoimmune diabetes in adults
MA	Metabolic acidosis
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MKA	Metabolic ketoacidosis
MTT	Meal tolerance test
NSAE	Non-serious adverse event
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
RMP	Risk management plan
SAE	Serious adverse event
SGLT2	Sodium-Glucose cotransporter-2
SmPC	Summary of Product Characteristics
SU	Sulfonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UKBP	Urine ketone body present
US	United States

1. Information on the procedure

1.1. Referral of the matter to the PRAC

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are indicated in the treatment of type 2 diabetes. Diabetic ketoacidosis (DKA) is a serious, often life-threatening condition, which usually develops in diabetic patients when insulin levels are too low, which switches the metabolic processing of glucose to that of fatty acids, in turn leading to the accumulation of acidic ketone bodies in the blood. A search in Eudravigilance (EV) database was performed in May 2015 by the European Medicines Agency (EMA) for the SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin. Several cases of DKA were identified in EV in diabetic patients for the three active substances, suggestive of a causal association. A safety warning on DKA was issued by the Food and Drug Administration (FDA) for this therapeutic class the same month. Taking into account the severity of these cases and the general pattern seen across these medicinal products, the European Commission (EC) considered that the risk of DKA and its impact on the benefit-risk balance of these products should be further investigated.

On 10 June 2015 the European Commission (EC) therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the Pharmacovigilance Risk Assessment Committee (PRAC) to assess the impact of the above concerns on the benefit-risk balance of canagliflozin-containing medicinal products (Invokana and Vokanamet), dapagliflozin-containing medicinal products (Forxiga and Xigduo), and empagliflozin-containing medicinal products (Jardiance and Synjardy) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are used together with diet and exercise in patients with type 2 diabetes mellitus (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, these substances cause more glucose to be removed via the urine, thereby reducing the levels of glucose in the blood via an insulin-independent mechanism. In the EU, the first SGLT2 inhibitor was authorised in 2012 and three SGLT2 inhibitors are currently authorised as mono-component and as fixed dose combination with metformin: canagliflozin (Invokana and Vokanamet), dapagliflozin (Forxiga and Xigduo) and empagliflozin (Jardiance and Synjardy). The exposure to these substances is respectively estimated to 565,000 patient-years, 555,470 patient-years and 66,052 patient-years worldwide.

Diabetic ketoacidosis (DKA) is a serious condition that usually develops when insulin levels are too low. In absence of insulin the metabolism switches from using glycogenolysis to lipolysis as a source of energy, which produces ketone bodies. Ketone bodies have a low pKa and therefore their accumulation in the blood lead to acidosis. This can be partially buffered with the bicarbonate buffering system, but this system is quickly overwhelmed and other mechanisms must work to compensate for the acidosis. In addition, the low levels of insulin along with a rise in plasma glucagon levels lead to the release of glucose by the liver. The glucose is partially excreted via the urine, leading to polyuria, dehydration, and compensatory thirst and polydipsia. DKA most commonly occurs in patients with type 1 diabetes mellitus (T1DM) and is usually accompanied by high blood glucose levels (>250 mg/dL). In a study that reported population-based rates of DKA, the incidence rate of DKA in T2DM patients, requiring

hospital admission, was reported to be 0.5 per 1000 patient-years (Wang,2008). The incidence of DKA in T1DM patients, is estimated to be 20 per 1000 patient-years, with approximately 3% of patients with T1DM initially presenting with DKA (Hamdy and Khardori 2014).

A search in Eudravigilance (EV) database was performed by the EMA on 19 May 2015 for the three SGLT2 inhibitors. One hundred and two (102) serious and sometimes life-threatening cases of DKA suggestive of a causal association were identified in T2DM patients for the three active substances, raising thus a safety signal. From the analysis of all identified cases, the time-to-onset of DKA is suggestive of causal association with these active substances. Published articles were also identified, describing a case of severe ketoacidosis associated with an SGLT2 inhibitor during a low-carbohydrate diet and a case of persistent glucosuria in the absence of hyperglycaemia 11 days after stopping canagliflozin. Overall, it was concluded that serious and sometimes life-threatening cases of DKA had been reported in patients on SGLT2 inhibitor treatment (canagliflozin, dapagliflozin or empagliflozin) for T2DM. In a number of these reports, the presentation of the condition was atypical with only moderately increased blood glucose levels observed. Atypical presentation of DKA in patients with T2DM could delay diagnosis and treatment. Cases of DKA were also reported in patients on SGLT2 inhibitors for T1DM, which is not an approved indication.

In view of the above, the EC considered that the risk of DKA and its impact on the benefit-risk balance of these products should be further investigated. In addition, the EC requested the EMA to give its opinion as to whether temporary measures are necessary to ensure the safe and effective use of these medicinal products. At the start of the procedure, based on the available information, the PRAC considered that temporary measures were not necessary and that the most effective risk minimisation activity at that point in time was a targeted communication to healthcare professionals via a DHPC. The PRAC and CHMP agreed on a DHPC, disseminated in July 2015, to increase the awareness of the possible occurrence of atypical DKA in T2DM and T1DM patients, and inform that an EU review was ongoing.

2.2. Clinical aspects

In its assessment, the PRAC considered all the data submitted from different sources. A summary of the most relevant data is included below.

No new efficacy data have been provided in the context of this review. All three substances were more effective than placebo at reducing HbA1c levels when used alone and in combination with other antidiabetic medicines. Treatment with canagliflozin, danagliflozin and empagliflozin as monotherapy and in combination with metformin or other antidiabetic agents led to clinically relevant improvements in fasting plasma glucose (FPG), body weight, and systolic and diastolic blood pressure.

The MAHs provided a cumulative review of all events of DKA (typical or atypical presentation) in association with their SGLT2 inhibitor product in clinical trials, literature and post-marketing. The reviews specifically focused on ketone, glucose and lactate levels, time to onset, dose including dose relationship, severity, predisposing factors, indication of the SGLT2 inhibitor (T1DM or T2DM), outcome and how the diagnosis of DKA was confirmed. The following MedDRA preferred terms (PTs) were 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.

2.2.1. Canagliflozin

2.2.1.1. Data from clinical trials

The MAH clinical trial safety database in T2DM consists of nine phase 3 studies that were part of the development plan of the product and seven randomised, controlled studies conducted since marketing authorisation, corresponding in total to 17,596 patients with approximately 10,687 patients treated with different doses of canagliflozin and 6,909 with a comparator. These studies provide approximately 23,943 subject-years, with 15,535 subject-years exposed to canagliflozin and 8,409 subject-years exposed to a comparator.

A search in this database ((DLP 11 May 2015), with the above-mentioned MedDRA retrieved 44 reports of DKA and related events in 43 subjects. Of these cases 17 were SAEs (serious adverse events) (including a subject who had a second serious DKA event 32 days after study discontinuation) and 27 non-serious adverse events (NSAEs). Twelve of the SAEs were severe, four SAEs were moderate, and one SAE was mild in intensity. Time to onset of event from initiation of canagliflozin ranged from a few days to years with most (75%) of the events starting after 245 days for SAEs and after 126 days for NSAEs. All the subjects with SAEs recovered from the events except for one subject on placebo with metastatic colon cancer who died from sepsis and respiratory failure during hospitalisation and one subject on another AHA who died from an acute MI following presentation with septic shock and acute kidney failure. All subjects with NSAEs recovered from the events except for four subjects with UKBP who had not recovered prior to the completion of the study. While study drug was discontinued or interrupted for the majority of subjects with SAEs, only 2 subjects with NSAEs had study drug discontinued or interrupted.

Ketone measurements were available for 7 SAEs and for 18 NSAEs (10 of the 18 measurements came from a single study in which routine measurements of urine ketone body were conducted). Bicarbonate values ranged from 1.8 to 15 mEq/L in the 10 SAEs for which it was measured, and from 12 to 27.5 mEq/L for the 15 NSAEs for which it was measured. pH measurements were available for 8 SAEs, ranging from 6.82 to 7.29, and for one NSAE, with a value of 7.23. Lactate was not elevated in the 2 SAEs for which it was measured (one acidosis and one DKA).

For the 14 SAEs where blood glucose measurements were available, blood glucose ranged from 8.2 to >27.8 mmol/L and were above 13.9 mmol/L in 11 SAEs (79%). For the 18 NSAEs where blood glucose measurements were available, blood glucose ranged from 5.1 to 24.8 mmol/L and was above 13.9 mmol/L in three cases (17%). Patients with T1DM were excluded from clinical trials but history of autoimmune diabetes or antibodies suggestive of autoimmune diabetes was present in 7 of the 15 subjects with SAEs and 3 subjects out of 16 subjects with NSAEs who were evaluated (antibodies were not available in one subject with a SAE).

Of the 16 subjects with SAEs, 12 were on insulin (alone or in combination with AHAs), 2 were on metformin alone, and 2 were on metformin and a sulphonylurea (SU). In contrast, 7 of the 27 subjects with NSAEs were on insulin and the remaining subjects were on oral AHAs either as monotherapy or in combination.

Precipitating or confounding factors can be identified in almost all the SAEs (94%), which included infection, MI, pancreatic or colorectal cancer, surgery, kidney and respiratory failure, reduction in insulin administration, noncompliance with treatment. In contrast, precipitating or confounding factors can be identified in a third (33%) of the NSAEs. Of the 10 subjects on canagliflozin with a DKA-related SAE, 8 were receiving insulin therapy with 6 having questionable compliance with insulin therapy at the time of the episode, 2 subjects having a concomitant diagnosis of MI, 1 subject having a cholecystitis which required a laparoscopic cholecystectomy, and 3 subjects with concomitant

diagnoses of pancreatic cancer, gastroenteritis, and viral infection. In the patients not on insulin with an event, 1 had T1DM; and 1 had a subcutaneous abscess and chronic pancreatitis.

The MAH calculated incidences using the 5 SAEs DKA cases and 16 DKA AEs in the 9,439 unblinded subjects available as of 31 July 2012. The MAH concluded that the incidence of DKA and related events was 0.2% in each canagliflozin group (5/3,092 patients treated with 100 mg/day canagliflozin, 7/3,085 with the 300 mg/day canagliflozin) relative to 0.1% in subject not treated with canagliflozin (4/3,262 in the comparator group). The incidence rate per 1,000 person-years were respectively 1.2, 1.8, 1.5 and 1.0 in the 100 mg/day canagliflozin, 300 mg/day canagliflozin, combined canagliflozin and comparator group. DKA SAE were reported in 0.1% (3/3,092 and 3/3,085) of the included in the canagliflozin groups (0.7 and 0.8 per 1,000 person-years in the 100 mg and 300 mg respectively) and <0.1% (1/3.262) of the patients in the non-canagliflozin group (0.2 per 1,000 person-years). In addition, as of 11 May 2015, when considering all unblinded cases from studies randomised on a 1:1:1 ratio (17,558 patients), 4 SAE were reported in the 100 mg group, 6 in the 300 mg group, 1 with another AHA and 1 with a placebo. The corresponding counts for NSAE are as follows: 5 in the 100 mg group, 11 in the 300 mg group and 6 in the control group. Of note the MAH reported incidence of DKA in T2DM estimated from 4 large US insurance claims databases, which varied widely with incidence rates between 0.32 and 2.00 per 1,000 patient-years.

The MAH also evaluated DKA case received from an 18-week phase 2 study in 351 patients with T1DM randomised on a 1:1:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg or placebo. There were a total of 12 SAEs and 6 NSAEs of DKA and related events in 17 subjects. All the affected subjects were on canagliflozin, with 5 SAEs and 1 NSAE occurring in the 100 mg dose group and 7 SAEs and 5 NSAEs occurring in the 300 mg dose group. One subject had a SAE of DKA and discontinued the study further to recurrence of UKBP (NSAE) after rechallenge with canagliflozin. Drug was withdrawn or treatment interrupted in all subjects except 1 subject with a SAE and 3 subjects with NSAEs. Bicarbonate and/or pH and/or ketone measurements supportive of the diagnosis were available in all 12 SAEs and in 5 of 6 NSAEs. For the SAEs, blood glucose ranged from 9.4 to >36.1 mmol/L and values were above 13.9 mmol/L in 7 SAEs (58%). SAE of DKA were reported in 4.27% (5/117) and 5.98% (7/117) and 0.0% (0/117) of patients on canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. Similarly, DKA and related events (serious and non-serious events) were reported in 5.1% (6/117), 9.4% (11/117), and 0.0% (0/117) of patients on canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively.

2.2.1.2. Post-marketing data

A search in the MAH's global safety database with a DLP 15 June 2015 using the requested MedDRA PTs retrieved 215 (208 serious, 7 non-serious) spontaneous report cases on patients treated with canagliflozin (including a duplicate excluded from further analyses). Review of the 85 DKA events with reported outcome indicates that 78 were resolved or resolving, and no events were reported to have a fatal outcome. Of the 214 cases, 93 patients had T2DM, 63 T1DM and 20 DM; diabetes type was not specified at all in the remaining cases. The time to onset of DKA, reported in 64 cases, was within a month in 33 cases, 2 months in 9 cases and between 3 months and a year in the remaining cases. The concomitant use of insulin prior to the onset of the DKA event was reported in 69 cases. In 66 cases with blood glucose result, 42 reported low levels (≤ 250 mg/dL or ≤ 13.9 mmol/L) or provided descriptive text (e.g. euglycaemic) to indicate atypically low blood glucose. Precipitating factors for development of DKA, including infection, dehydration, surgery, renal and respiratory failure, weight loss before the event, reduced carbohydrate intake, alcohol use and reduction in insulin administration were reported in 95 cases. The analysis of post-marketing data for DKA identified a slightly higher frequency of cases reporting the 300 mg dose of canagliflozin.

The additional 4 cases in T2DM patients who received canagliflozin/metformin reported the PT acidosis and the PT DKA with equal frequency. Event outcome was reported for 2 of the 4 DKA events, and both events were considered resolved. All the cases were reported by a heath care professional and all but one were serious. Of the 4 cases, 1 case reported a blood glucose result (≤13.9 mmol/L). Time to onset of the event was reported as 5 days in 1 case and 4 months in another. Among the 4 cases, 1 case reported use of a dietary supplement to decrease glucose levels in preparation for surgery as a possible precipitating factor for the development of DKA.

2.2.1.3. Literature

The MAH also identified three publications discussing DKA cases in patients treated with canagliflozin. Two publications reported cases a DKA case with atypically low blood glucose level, which delayed recognition of the problem by patients and healthcare professionals alike (Hilaire, 2015; Peters, 2015). The great majority of the subjects presented with precipitating factors. A third publication however reported in the analysis of all (12) SAEs of DKA and related events from randomised studies of canagliflozin in 17,596 T2DM patients that most patients had a blood glucose >16.7 mmol/L at presentation of DKA (Erondu, 2015).

2.2.2. Dapagliflozin

2.2.2.1. Data from clinical trials

The clinical trial safety database, constituted pooled patients of 21 completed active- or placebo-controlled studies (phase 2b and 3) performed in subjects with T2DM, consisting of 5,936 subjects treated with dapagliflozin (2.5 mg, 5 mg, 10 mg, 20 mg, or 50 mg) and 3,403 subjects on control treatment (either as monotherapy or in combination with other antidiabetic therapies). The total exposure was 6,247 patient years for dapagliflozin and 3,638 patient-years for controls.

There were 4 reported events with the requested MedDRA PTs in subjects on dapagliflozin in clinical trials included in this database. A subject treated with dapagliflozin 10 mg, metformin and insulin was hospitalised on day 214 after experiencing vomiting, diarrhoea, exsiccosis, acidosis, weakness, and discomfort. Diagnosis of gastroenteritis and DKA was based on urine analysis, blood gas analysis, glucose measurement, ECG and other laboratory test. Dapagliflozin treatment was interrupted temporarily until resolution of the event, no recurrence was observed. One non-serious metabolic acidosis reported at day 396 in a subject treated with dapagliflozin 10 mg, SU, and thiazolidinedione. Two NSAE cases of ketonuria occurred in two patients of the same study, respectively on day 79 and 124, in the first patient the event resolved after 20 days, this information was not available for the second patient however no change to treatment was needed until end of the study. Urinary ketones were not monitored as part of the trial. In addition, a subject treated with dapagliflozin 20 mg experienced a metabolic acidosis SAE 20 days after end of treatment. The subject appeared weak, complained of no appetite and diarrhoea, and the self-glucose monitor showed 190 mg/dL. Laboratory evaluation showed arterial blood gas values consistent with a metabolic acidosis.

The MAH estimated the incidence for DKA only from the clinical development programme to be 0.016% (95% CI: 0.0038%, 0.059%) and for DKA/metabolic acidosis to be 0.032% (95% CI: 0.0099%, 0.089%) which corresponds to 0.16 per 1,000 patient-years for DKA only and 0.32 per 1,000 patient-years for DKA/metabolic acidosis. The MAH identified only one study (Wang, 2008) that reported population-based rates of DKA for T2DM patients. In this study the incidence rate of DKA requiring hospital admission was reported to be 0.50 per 1,000 patient-years. The MAH also conducted a study of the Humedica/Optum Diabetes database to assess the incidence of DKA in T2DM patients residing in

the US 2011-2013 and calculated the following incidences: 0.06% for 2011, 0.05% for 2012, and 0.07% for 2013.

In subjects with T1DM, reported incidence of DKA in the literature ranges from 1.5% to 26%. Since T1DM is not an authorised indication for dapagliflozin, there are, for the moment, no figures available from clinical development programme.

2.2.2.2. Post-marketing data

The MAH also conducted a search with a DLP 15 June 2015 in its global safety database, which contains all adverse event reports from spontaneous sources (e.g. healthcare professionals, regulatory authorities, literature and patients) and well as SAE reports from clinical trials. This search identified 90 case reports, 87 for dapagliflozin and 3 for dapagliflozin in combination with metformin. Of the 90 cases, 48 were reported in T2DM patients, 19 in T1DM and for 23 the type of diabetes was not reported. Of the 87 dapagliflozin case reports, 84 were from spontaneous reports, 2 from clinical trials, and 1 from a post-marketing program. Of the 3 reports for dapagliflozin/metformin, 2 were spontaneous reports and 1 was from a post-marketing program. In these 90 case reports, there were 91 adverse events related to the terms listed above (MedDRA PTs): DKA (47), K (30), MA (5), A (3), BKBI (3), K (2) and UKBP (1). Out of the 90 case reports, 89 were medically confirmed. All cases were defined as serious with the exception of one non-serious case report. There were 29 men, 47 women, and 14 patients for whom gender was not reported. Age was reported in 61 of the case reports, with a mean value of 52.1 years (range 14 to 86 years).

Three of the case reports had a fatal outcome. A patient with poorly controlled T2DM managed by insulin pump died while on treatment with dapagliflozin and insulin, possible cause of death was reported as DKA or hypoglycaemia with however no documented investigations supporting either diagnosis. A second patient, hospitalised for DKA while on treatment with dapagliflozin and metformin, was reported to have died from fatal pulmonary and bone metastases approximately 2 months later. The reported cause of death for the third patient was asphyxiation due to bacterial pneumonia, but the report also includes possible ketoacidosis at the time of death.

In the 90 case reports the information was generally limited:

Forty-eight case reports describing 49 AEs were retrieved in patients with T2DM: DKA (27), K (12), MA (4), BKBI (3), A (2), UKBP (1). Thirty-eight events let to hospitalisation while two events were non-serious. Eight case reports included information on intensity: 4 were reported as severe, 3 were reported as moderate, and 1 was reported as mild. Outcome was reported in 33 cases; 24 were reported as recovered, 8 were reported as recovering and 1 case was reported with fatal outcome (patient with poorly controllled T2DM described above).

Thirty case reports included information on symptoms normally associated with ketoacidosis such as nausea, vomiting, malaise, dehydration, dizziness, abdominal discomfort, weight loss and tiredness. Several of the case reports describe changes in food and fluid intake in connection to the development of acidosis, such as gastroenteritis, limited carbohydrate diet, decreased intake in connection to surgery, or nausea reported as side effect to other medications. Some of the case reports also described patients with poorly controlled diabetes.

Information on time to onset of the event following initiation of dapagliflozin treatment was reported in 36 cases: within 1 to 2 days in 4 cases, within approximately 1 week in 6 cases, within approximately 1 month in 10 cases, within approximately 6 months in 9 cases, and after longer than 6 months in 5 cases. Dose was reported in 36 of the case reports: 23 were reported to be on 10 mg per day, 12 were reported to be on 5 mg per day and one was reported on 20 mg per day. Twenty case reports contained information on insulin treatment, 15 case reports contained information on sulfonylurea use,

and 29 included information on metformin use. Of these, 8 case reports included information on dose changes; 5 changed insulin and 3 changed sulfonylurea dosing. Twenty case reports included information on blood glucose values; 14 of these had normal or near-normal values (below 250 mg/dL or 14 mmol/L). Twenty-seven of the case reports contained information on one or several laboratory findings (pH, bicarbonate, ketones, lactate).

Nineteen case reports were identified for patients receiving dapagliflozin as off-label treatment for T1DM (including 2 patients stated to be diagnosed as both T1DM and T2DM). Time to onset of ketoacidosis after initiation of dapagliflozin treatment was reported as 1 day, 5 days, "several" days and approximately 2 months (not reported in 15). One patient was on 5 mg/day was and 3 on 10 mg/day (not reported in 15). Five cases were reported as severe (not reported in 14). Ten of the events led to hospitalisation. Fifteen of the events were reported in adult patients and one in an adolescent. Limited information on the cases was available. Six patients were reported to be recovering or to have recovered (not reported in 13). Information on insulin use was included in 6 reports and in 4 of these reports, there was information on omission of insulin or reduced insulin doses. Concomitant use of metformin was reported in 3 cases (not reported in 16).

Only 3 of the reports included information on urinary ketones and/or pH. Blood glucose was reported for one of these cases (267 mg/dL). In 2 cases, normoglycaemia or euglycaemia was stated and in two additional cases blood glucose was described as normal or near-normal (below 250mg/dL or 14 mmol/L). One case report stated the prescription was for weight loss and in another case report dapagliflozin was given in combination with ketogenic diet.

For 23 patients with DKA (12), KA (8), A (1), K (1, not recovered), MA (1, not recovered) the type of diabetes was not recorded. Two reports described development of ketoacidosis: 1 in connection to convulsion, sepsis, and presence of bone/pulmonary metastasis, and 1 in connection to alcohol intoxication and coma. The time to onset of ketoacidosis after initiation of dapagliflozin treatment was within a few weeks in 1 case, within 1 to 2 months in 1 case, within 2 to 3 months in 1 case, and after longer than 2 months in 2 cases (not reported in 18). Nine patients were treated with 10 mg/day dapagliflozin, and two with 5 mg/day (not reported in 15). Seven case reports inlcluded information on insulin treatment; 5 of these reported dose changes. One of these 5 case reports also reported sulfonylurea treatment which was stopped. Information on concomitant metformin use was reported in 7 case reports. One case report contained information on pH and bicarbonate. Three case reports included information on blood glucose values; of which 2 had normal or near normal values.

The above information from spontaneous reporting was further confirmed by the 181 cases received between 15 June 2015 and 4 October 2015. Out of those case reports, 49 included information on insulin therapy. A number of those case reports included information that insulin doses had been reduced or insulin therapy stopped prior to the event; several case reports included information on other possible precipitating factors such as infections, operative procedures or changes in diet. Forty-three (43) reports contained information about blood glucose levels and in 30 of these cases blood glucose were reported to be below 14 mmol/L (250 mg/dL).

Two of the above cases of T2DM patients presenting with DKA symptoms, normal glucose values and undiagnosed pancreatic insufficiency were described by Hine et al. (2015) who discussed the significance of euglycaemic DKA in patients taking SGLT2 inhibitors and described that SGLT2 inhibitor act as an insulin-independent regulator of glucose concentrations through increased renal excretion. Renal glucose filtration increases in proportion to plasma glucose concentration; thus, a normal plasma glucose concentration can be maintained in absolute insulin deficiency by increasing glycosuria.

2.2.3. Empagliflozin

2.2.3.1. Data from clinical trials

The MAH preformed first a narrow search with the PT ketoacidosis, diabetic ketoacidosis, diabetic ketoacidotic hyperglycaemic coma and acetonaemia, in its clinical trial safety data pool including all T2DM patients treated within the empagliflozin clinical development programme, including 13,605 randomised and treated patients, 8,756 of them treated with empagliflozin.

The narrow search identified 8 cases of DKA or ketoacidosis, out of which 3 patients received empagliflozin, 5 patients received placebo, and no case was identified on active comparators. The first of these 3 patients, on 10 mg empagliflozin, was diagnosed on Day 535 based on positive urine ketone bodies without clinical symptoms. The second patient was treated with empagliflozin 10 mg as an add-on to insulin and developed serious events of DKA on Day 111 and seizure. This patient showed a negative c-peptide test result, indicating a low β-cell function reserve. The study medication was discontinued. The third patient chronic/recurrent urinary tract infection was treated with empagliflozin 25 mg and background insulin. On Day 47 the patient was hospitalised for hyperglycaemia with fatigue, nausea, vomiting, weakness and headache, and diagnosed with non-serious DKA. The study medication was temporarily interrupted and restarted once the patient had recovered. No information is available about specific diets for those patients. The overall clinical presentation of those 3 events does not seem to differ from the clinical presentation of the 5 placebo events. There was no clear pattern of DKA under empagliflozin treatment identified by this narrow search for DKA.

A broader search including ‘acidosis’, ‘metabolic acidosis’, ‘ketosis’, ‘ketonuria’, ‘urine ketone body present’ and ‘blood ketone body present’ retrieved 11 additional events in patients treated with empagliflozin and 5 in patients treated with a placebo. No imbalance of those additional events identified by was observed between patients treated with empagliflozin 10 mg (5 events), empagliflozin 25 mg (6 events), and placebo (5 events). None of these events were assessed as being a DKA after medical review.

In clinical trials in T1DM patients, including 117 patients, the narrow search identified 2 DKA events in the same study (open-label, single arm of empagliflozin as adjunctive treatment in 40 adults). One patient had severe gastroenteritis prior to the DKA event and the other experienced DKA due to insulin pump failure. In these cases, according to investigator judgement and in response to capillary glucose readings, total insulin doses were reduced by 70% and 50% of pre-treatment levels shortly after initiating empagliflozin treatment. One patient presented with nausea and vomiting, plasma glucose measured at 17.0 mmol/L and blood pH of 7.01. The other patient presented nausea with a plasma glucose reading of 11.8 mmol/L and blood pH of 7.26. Both patients fully recovered.

2.2.3.2. Post-marketing data

A cumulative search in the MAH safety database was performed for any spontaneous cases reported as ‘Diabetic Ketoacidosis’ until 17 October 2015. The search strategy for DKA events was based on a narrow and broad search as described above. The narrow search retrieved 60 spontaneous case reports (of which 42 were reported after 13 June 2015). The broad search identified another 7 reports, one of which was assessed as DKA after medical review and was added to the cases retrieved with the narrow search. Between 18 October 2015 and 10 December 2015, 24 additional DKA cases were received, identified by the narrow scope search, including one fatal case in a patient with latent autoimmune diabetes of adults (LADA) and one case in a patient on 12.5 mg/1000 mg empagliflozin/metformin per day.

Up to 17 October 2015 there were 51 spontaneous cases reported as DKA with empagliflozin including 2 fatal cases in T2DM patients. A male patient with T2DM developed DKA 2 weeks after start of empagliflozin, the patient died due to DKA, aspiration and renal failure on ICU. The second male patient with T2DM had ketoacidosis within the context of a sepsis, was hospitalised about 3 weeks after treatment initiation and died of a heart attack one week later. There were 26 female patients (age range 17 to 71 years; no age was reported for 7 female patients) and 24 male patients (age range 21 to 62 years; no age was reported for 5 male patients). No gender and age were reported for 1 patient with events related to DKA.

Out of the 30 cases were T2DM was specifically reported 14 patients were on 10 mg/day, 7 on 25 mg/day and for 9 the empagliflozin dose was not reported. Concomitant treatment with insulin was reported in 5 cases, with metformin in 11 cases and both in 6 cases. In 5 cases concomitant treatment with DPP4-inhibitors was reported, in 4 cases SU and in 2 cases GLP-1 analogues were reported in addition to insulin and/or metformin as concomitant medication. One of these patients had signs and symptoms of DKA already prior to treatment start and was finally treated with insulin. Precipitating factors were reported in 9 cases: serious infection (sepsis, pneumonia, viral infection) in 4 cases, weight loss/diet conditions in 5 cases. In 4 cases dehydration was reported; however, it is not clear if dehydration occurred as precipitating factor or as a sign of reported DKA. No information on confounding factors was provided in 16 cases.

Eleven cases corresponded to off-label use in patients with T1DM. Four of those patients were on 10 mg/day empagliflozin, 5 on 25 mg/day and for 2 patients the dose was not specified. Precipitating factors were reported in 5 cases: acute pancreatitis in one case, weight loss/diet conditions in 2 cases, discontinuation of insulin in 2 cases. In 2 cases dehydration was mentioned; however, it is not clear if dehydration occurred as precipitating factor or as a sign of reported DKA. No information on confounding factors was provided in 4 cases.

In 10 cases the indication for empagliflozin treatment was unclear diabetes (no type provided in 3 cases) or completely unknown (in 7 cases). Three patients were treated with 10 mg/day, 3 with 25 mg/day and for 4 patients, the dose was not specified. Concomitant treatment with insulin was reported in 4 cases, with metformin in 1 case and with both in 2 cases. In 2 cases concomitant treatment with DPP4-inhibitors was reported, in one case SU and in 2 cases GLP-1 analogues were reported in addition to insulin and/or metformin as concomitant medication. Precipitating factors were reported in 2 cases: severe hypotension and acute renal failure in one case and post coronary artery bypass surgery (CABG-OP) in one case. No information on confounding factors was provided in 8 cases.

2.2.4. Discussion

The MAHs submitted information on DKA-associated cases concerning both T1DM and T2DM patients, mainly from clinical trials and spontaneous reports.

Forty-three reports of DKA and related events in 43 subjects were identified in the clinical trial of canagliflozin programme including 17 SAE and 27 NSAE. However, some SAEs have been classified as serious due to the hospitalisation of patients for concomitant events, not related to DKA e.g. surgery, cancer or pneumonia. DKA and related events have occurred at a low frequency over time in subjects with T2DM participating in canagliflozin clinical trials. The MAH estimated the incidence of DKA and related events to 0.2% in each canagliflozin group relative to 0.1% in subject not treated with canagliflozin and the incidence of DKA SAE to 0.1% in the canagliflozin groups and <0.1% in the non-canagliflozin group. The incidence of these events is within the range expected when compared with existing observational data in the general population with T2DM. The MAH incidence calculation should

be carefully considered as they do not appear to follow international standard and might have slightly overestimated the incidence. In addition, the pooled data includes unblinded parts of a large study in patients with higher morbidity, in which most of the SAEs were reported. The incidence of DKA in T2DM estimated from 4 large US insurance claims databases varied widely, with incidence rates between 0.32 and 2.0 per 1,000 patient-years.

The incidence rate of DKA seen with dapagliflozin in T2DM patients (0.16 per 1,000 patient-years for DKA only and 0.32 per 1,000 patient-years for DKA/metabolic acidosis), as judged from clinical trial data, is not higher than expected based on incidence rate reported in the literature (Wang, 2008). However, since the population in the development programme is probably somewhat different than populations in epidemiological studies in other aspects than dapagliflozin-treatment, it is not possible to draw definite conclusions based on the comparison that MAH has presented. The incidence data from the Humedica/Optum database studies (ranging from 0.05% to 0.07%) are presented in a way that precludes a direct comparison with incidence data estimated from the clinical trials but at least the magnitude of the figures does not cause additional concerns. Of note nevertheless, in the dapagliflozin clinical trials, no DKA, ketonuria or metabolic acidosis was reported in the control groups. Estimated incidences based on spontaneous reports were not considered meaningful.

Eight cases of DKA or ketoacidosis were identified in the empagliflozin clinical trials, out of which 3 patients received empagliflozin, 5 patients received placebo, and no case was identified on active comparators. The event rates were 0.2 per 1000 patient-year for empagliflozin 10 mg, 0.9 per 1000 patient-year for empagliflozin 25 mg and 1.5 per 1000 patient-year in the placebo group. Although interpretation is limited by the low number of events, no imbalance is observed in clinical trials. In addition, the overall clinical presentation of the DKA events during empagliflozin treatment did not differ from the overall clinical presentation of the events during placebo. The MAH estimated that the reporting rate for spontaneous rates of DKA for empagliflozin is approximately 0.3 per1000 patient-years. Based on data insurance claims databases from the United States, the MAH estimated the proportion of patients with T2DM to be 4 - 8 per 1000 patient-years. Although data from insurance databases cannot be directly compared with clinical trials and spontaneous reporting, the risk of DKA with empagliflozin did not appear higher than the estimated background risk.

The data provided does not rule out a small excess risk of DKA-related events in T2DM-patients on SGLT2-inhibitors. Overall, the number of cases was low. Incidences cannot be directly compared between products as they have not all been computed using the same methodology and patients including in the clinical development program may not share the same baseline risk for DKA. However, due to the low number of events and considering the plausible common mechanism behind SGLT2-induced DKA, there is no clear indication that the risk substantially differs between the products. The PRAC was of the view that DKA should be added to the product information (PI) of these products with the frequency ‘rare’.

The analysis of the cases is hampered by the limited information provided in the reports and potential for reporting bias regarding some aspects of the clinical presentation. However, acknowledging these limitations, it is still noteworthy that in a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l. In contradiction with these findings and previously reported results, glucose levels were above the 13.9 mmol/L (250 mg/dl) threshold in most of the SAE cases in canagliflozin clinical trial. This may be partially explained by the history of autoimmune diabetes or antibodies suggestive of autoimmune diabetes present in 7 of the 15 patients with SAEs were this test was conducted. Patients with autoimmune diabetes are considered to be at higher risk of DKA than T2DM patients. Overall, the clinical presentation of DKA in SGLT2-inhibitor treated patients is in many cases atypical with relatively low glucose levels, which may increase the risk of late diagnosis by patients and doctors, delay in appropriate treatment, and as a

consequence, potential development of a more severe stage of DKA. The PRAC is therefore of the opinion that the risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

Known factors associated with DKA include a low beta-cell function reserve (T2DM patients with low C-peptide or LADA or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. In the currently available data on patients treated with SGLT2 inhibitors, the risk factors reported match the well-known initiating factors common to the diabetic population. These should therefore be added to the PI in order for patients to consider those before initiating treatment and for patient to be aware of behaviour that may increase DKA risks. Most of these risk factors are transient or predictable. Therefore, a temporary interruption of SGLT2 inhibitor treatment may be sufficient in most of the cases to reduce the risk of DKA. There may also be an increased risk of DKA in patients who have experienced DKA while on SGLT-2 inhibitor treatment. Therefore, restarting SGLT2 inhibitor treatment in these patients is not recommended, unless another precipitating factor is identified and resolved. Treatment should also be temporarily interrupted in patients with T2DM who are hospitalised for major surgical procedures or acute serious medical illnesses.

Other antidiabetic drugs, such as metformin, DPP-4 inhibitors, or SUs, are not reported to have an increased or decreased risk for DKA. However, prolonged omission of oral hypoglycaemic therapy could increase the risk of DKA. DPP-4 inhibitors in combination with SGLT2 inhibitors have the potential to lower the glucagon/insulin ratio, but the clinical relevance for a decrease in the risk to develop DKA is unknown.

While the majority of subjects with DKA SAEs were on insulin therapy in canagliflozin clinical trials, over 5,000 subjects were on insulin in the development trial (Erondu, 2015). Therefore, use of insulin cannot be used to identify specific individual patients at risk for developing DKA but rather may simply be an indicator of patients with significant loss of pancreatic beta-cell function or insulinopenia. Furthermore, no clear pattern can be identified with respect to the role of concomitant use of other AHA agents (eg, metformin, DPP-4i, or SU) along with canagliflozin in the risk of DKA.

The only reported case of DKA in the clinical development programme of dapagliflozin occurred in a patient on insulin treatment who also received metformin. In spontaneous reports of ketoacidosis-related AEs in patients on different diabetes treatments in the MAH safety database up to 04 October 2015, out of 271 patients, 77 were treated with insulin, 126 with Metformin, 38 with SU and 30 with DPP-4 inhibitors. One hundred and twenty eight (128) patients received ‘other treatment’ which means that the case report contained no information on treatment with any of the four previously mentioned treatments.

Out of the 7 patients with events of DKA on empagliflozin treatment in the clinical trials, 5 patients received concomitantly insulin and 3 patients concomitant metformin treatment (of which 3 patients were treated with both, insulin and metformin). No patient with DKA was identified with DPP-4 inhibitors or SU as concomitant anti-diabetic therapy add on to empagliflozin. Post-marketing data comprised 49 cases of DKA in T2DM. Patients were treated with insulin (21 cases) and metformin (23 cases). Out of these, in 9 cases the combination of insulin and metformin was reported as concomitant medication. Concomitant medications in addition to insulin and/or metformin were DPP-4 inhibitor (9 cases), SU (5 cases) and GLP-1 analogue (4 cases).

In T2DM patients, the absolute number of DKA SAE observed in unblinded patients increased with the dose of canagliflozin, however, no conclusion can be drawn from the currently available data. A majority of the spontaneous reports in the MAH's safety database which include information on dose, concerns the 10 mg/day dapagliflozin, however as this is the dose primarily used in the EU, no conclusions can be drawn regarding dose relationship from the available data. There were small dose-dependent increases in ketone body levels observed in trials in patients treated with SGLT2 inhibitors. However, no dose dependent increase of the incidence of DKA events was observed in the empagliflozin clinical trials.

The current information on DKA occurring during SGLT2 treatment relies on a limited number of poorly documented cases, which limits the possibility to distinguish subpopulations at risk or specific risk factors, including concomitant treatment. Further analysis of the data currently available is not expected to allow more robust conclusions. Considering that the data available from clinical trials and pharmacovigilance activities did not allow to conclude that the risk of DKA with SGLT2 inhibition is different in monotherapy than when used in combinations such as metformin, DPP-4 inhibitors, or SU, dedicated interaction studies are not considered needed at this stage, however, further analysis of DKA cases with regard to interactions should be included in ongoing or planned studies (see risk management section below).

Regarding insulin it is probably not insulin therapy in itself but rather the need for insulin therapy in the T2DM patient that increases the risk for DKA. This need reflects declining β cell function and confers a risk of absolute or relative insulin deficiency in situations where the need is not met. Omission of, or inadequate insulin therapy is a known precipitating factor for DKA. However, simple omission may not be sufficient for the development of DKA, unless accompanied by a concomitant rise in plasma stress hormones (Schade and Eaton 1983).

Overall, patients with T1DM were more closely monitored than T2DM patients with regard to laboratory parameters for DKA in clinical trials with canagliflozin. Glucose levels were above 13.9 mmol/L in only 58% of the SAE cases compared to 78% in T2DM patients. The numerical imbalance with regard to DKA between the canagliflozin group (18 DKA) group and comparator group (0 DKA) is more pronounced in this trial compared to the T2DM trials. In addition, one case of positive rechallenge suggestive of a causal relationship was observed. Post-marketing, 20% of reported cases related to off-label use of canagliflozin in T1DM patients. Dapagliflozin has not been studied in clinical trial in type 1 diabetes. Two of the 117 T1DM patients in ongoing clinical trials with empagliflozin experienced DKA. There is no indication that the risk of DKA in T1DM during treatment with empagliflozin or dapagliflozin is lower than that with other SGLT2 inhibitors. Therefore, it should be included in the PI that limited data from clinical trials suggest that DKA occurs with common frequency in these patients. In addition, it should be reminded that the safety and efficacy of SGLT2 inhibitors-containing products have not been established in patients with T1DM and they should not be used in this population.

In conclusion, while a small excess risk of DKA cannot be excluded in T2DM patients treated with DKA, the incidence remains low. However, the possible occurrence of cases presented atypically should be included to the PI in order to allow early recognition of the events and prompt treatment. Information currently available is limited, however additional pharmacovigilance activities are expected to provide relevant data to further characterise this risk.

2.3. Mechanistic aspects

2.3.1. Possible mechanisms

The MAHs were asked to discuss potential mechanisms by which SGLT2 inhibitors could induce DKA. Although the underlying mechanisms for a potential SGLT2 inhibitor-associated increase in ketone bodies are not fully established, several known effects of SGLT2 may contribute to ketone production.

A common view emanating from the responses from all three MAHs (either based on non-clinical or clinical observations) is that SGLT2 inhibitors may increase levels of ketone bodies by affecting glucagon/insulin ratio and lowering plasma glucose levels (Ferrannini 2014; Merovci 2014; Stein 2014). These conditions could alter hepatic metabolism to favour ketone body production, especially under fasting conditions when glycogen stores are depleted. This implies that SGLT2 inhibitors could augment the rate of hepatic ketone production in addition to other known causes of DKA, such as fasting and low carbohydrate intake. Although the increases in ketone bodies measured in preclinical models as well as those observed during clinical trials were mild or modest and did not seem to cause acidosis under normal conditions, a combination of risk factors of specific conditions such as very low carbohydrate diet may exacerbate ketone body production up to levels which may lead to acidosis. SGLT2 inhibitors are also known to lead to increased water loss, a known factor in ketoacidosis.

Literature also suggests that SGLT2 inhibitors may have a direct effect on pancreatic α-cells causing glucagon release (Bonner, 2015).

In addition to the mechanisms already mentioned above, Taylor and colleagues (2015) recently suggested that marketed SGLT2 inhibitors may reduce renal clearance of ketone bodies, by enhancing the tubular reabsorption of ketones filtered from the plasma. That effect was suggested as an additional mechanism by which SGLT2 inhibitors might exacerbate ketonemia in the setting of clinical situations that trigger DKA (eg, insulin deficiency or stress). Taylor et al. (2015) point out that the Na-monocarboxylate transporter-1 (SLC5A8 or SMCT1) which mediates Na-linked uptake of acetoacetate and beta-hydroxybutyrate (Martin 2006), is expressed in the proximal renal tubule (Becker, 2010), and speculated that reduced Na-glucose reabsorption in the proximal renal tubule (due to inhibition of SGLT2 transporters) would increase luminal Na concentrations and thereby drive greater Na-linked reabsorption of filtered ketone bodies via SLC5A8. If true, SGLT2 inhibitors might increase plasma ketone body levels not only by increasing the glucagon/insulin ratio and increasing hepatic ketone production (as described earlier), but also by reducing renal ketone body clearance - with both effects together accelerating development of clinical DKA. Reduced renal ketone clearance might also affect detection of urine ketones, often used as an early sign of rising plasma ketone levels.

The data provided by the MAHs were not sufficient to support or dismiss these mechanistic hypotheses.

2.3.2. Available non-clinical data

According to the MAHs, ketone bodies were not measured in animal toxicity studies after administration of dapagliflozin or canagliflozin. They were however measures in normal and type 2 diabetic ZDF rats in pharmacological studies with empagliflozin. A few published data are also available on diet-induced obese rats treated with dapagliflozin and SD or Wistar rats under high fat diet treated with tofogliflozin or ipragliflozin, respectively.

The results from the preclinical studies showed that treatment with SGLT2 inhibitors mimics fasting conditions, by decreasing blood glucose levels in parallel to insulin levels, by switching the energy source from carbohydrate oxidation to fatty acid oxidation and by promoting the use of fatty acids as ketone body precursors. During treatment with SGLT2 inhibitors, the plasma levels of ketone bodies

were further increased under fasting condition, while under non-fasted condition the augmentation of ketone bodies was not detectable or very moderate. Additional experiments performed with empagliflozin indicated that following an overnight fast, refeeding empagliflozin-treated rats with lipids causes a higher ketone body burst than after refeeding with glucose.

2.3.3. Discussion

The pathophysiological mechanisms that lead to a SGLT2 inhibitor induced ketoacidosis is not well characterised and the MAHs should endeavour to clarify the mechanism behind SGLT2-induced DKA occurrence.

Non-clinical mechanistic studies are already planned or on-going for dapagliflozin- and empagliflozin-containing products. Such study is also required to be undertaken by the MAH of canagliflozin-containing products.

3. Benefit-risk balance

When considering all the data submitted by the MAHs from clinical and non-clinical studies, post-marketing reports and from published literature, in relation to the risk of DKA in association with SGLT2 inhibitors, the PRAC was of the view that a small excess risk could not be excluded in patients with T2DM. DKA typically occurs in T1DM patients with high blood glucose concentrations. However, cases reported with SLGT2 inhibitors occurred in patients with T2DM as well as T1DM. Further, in a number of cases, blood glucose values were only moderately increased or normal. DKA cases were reported in all three SGLT2 currently authorised in the EU, suggestive of a class effect. Although the MAHs estimated slightly different incidence rates, these were not all calculated according to the international standards for computation of incidence rate. Further, different inclusion and exclusion criteria were used in the clinical development programs of the products, therefore the populations may not share the same baseline risk of DKA and careful consideration should be given to any direct incidence comparison. Based on the data available, the PRAC considered that there was no indication of a different risk between the products. This is further supported by the likely common mechanism of action. Considering the above, the PRAC was of the view that DKA should be included in the PI of all SGLT2 inhibitors with the frequency rare.

The atypical presentation of DKA cases in SGLT2 treated diabetes patients, combined with the otherwise non-specific symptoms presented by patients with DKA may delay the diagnosis and therefore lead to the development of more serious or life-threatening conditions. In order to minimise this risk, the PRAC considered that physicians and patients should be warned through the PI to consider the risk of atypical DKA in the occurrence of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness, even in absence of hyperglycaemia. Patients should be advised to contact a doctor in order to be tested for ketoacidosis and to discontinue SGLT2 inhibitor treatment if DKA is suspected or diagnosed.

In addition, the PRAC considered that “DKA with atypical presentation” should be added as an important identified risk to the Risk Management Plan (RMP) of those products. Several post-authorisation safety studies are planned or ongoing in order to compare the incidence of DKA in SGLT2 inhibitors and other anti-hyperglycaemic agents. In addition, the MAHs are required to clarify the mechanism behind SGLT2 inhibitors-induced DKA. Non-clinical mechanistic studies are already planned or on-going for dapagliflozin- and empagliflozin-containing products; such study is also required to be undertaken by the MAH of canagliflozin-containing products. A non-clinical mechanistic study protocol is required to be submitted by the MAH of canagliflozin-containing products for review by the PRAC,

within 6 months of adoption of the CHMP opinion. Those studies are expected to enable better characterisation of the risk of DKA and its mechanism and should be included in the RMP of those products. Moreover, the MAHs should explore the feasibility of collecting plasma hormones in new or ongoing trials with the aim to identify patterns of hormone derangement that could further explain the mechanism of action of SGLT2 inhibitors in ketoacidosis.

The PRAC further concluded that a risk of DKA, with or without atypical presentation, is associated with SGLT2 inhibitors treatment in patients with T1DM. This is not an approved indication for SGLT2 inhibitors containing products. Limited data from clinical trials suggest that DKA occurs with common frequency in T1DM patients. The PRAC considered that this information should be included in the PI and, considering that the safety and efficacy of SGLT2 inhibitors have not been established in patients with T1DM, healthcare professionals should be reminded that these should not be used in this indication. Planned and ongoing Drug Utilisation Studies (DUS) for dapagliflozin- and empagliflozin-containing products are expected to generate more information on the extent and nature of the off-label use. All MAHs are required to submit the final study report to the EMA as they become available. In addition, a DUS, ideally based on secondary observational data via existing databases, is also required to be undertaken by the MAH of canagliflozin-containing products. A DUS protocol is required to be submitted by the MAH of canagliflozin-containing products for review by the PRAC, within 6 months of adoption of the CHMP opinion. The RMP of all these products should be updated accordingly, within 3 months of adoption of CHMP opinion.

The relatively long time-to-onset observed in clinical trials is suggestive of contributing factors triggering the development of DKA. Moreover, risk factors reported in the cases are consistent with those previously reported in the literature and the risks factors inherent to the patient population (e.g. patients with low beta-cell function reserve, restricted food intake or severe dehydration, sudden reduction in insulin dose and increased insulin requirements due to acute medical illness, surgery or alcohol abuse). The PRAC considered that these should be included in the product information and physicians advised to consider the patient's history before initiating treatment with SGLT2 inhibitors. In addition treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Further, restarting SGLT2 inhibitor medication in patients with previous DKA while on treatment is not recommended unless another clear precipitating factor is identified and resolved. No subset of the population at increased risk could be identified from the analysis of cases reported in clinical studies. No definite conclusion could be drawn regarding dose relationship or protective or exacerbating effect of concomitant medicines. Overall the reported cases were poorly documented and the MAHs are requested to implement targeted follow up questionnaires, in order to document consistent information on the cases. The results of these targeted follow up questionnaires should be discussed in the next PSURs.

The PRAC considered that the efficacy of these products had been adequately demonstrated in their currently authorised indications in monotherapy and in combination as an adjunct to diet and exercise to improve glycaemic control in T2DM adult patients.

In conclusion, the PRAC considered that the benefit-risk balance of SGLT2 inhibitors-containing products remained favourable, provided the proposed changes to the product information and the risk management plan are implemented.

4. Risk management

The PRAC considered that “diabetic ketoacidosis with atypical presentation” should be included as important identified risk in the RMP for all SGLT2 inhibitors. The below ongoing and planned activities are considered relevant to better characterise this risk and should be included in the RMP. An updated RMP should be submitted within 3 months of adoption of CHMP opinion.

4.1. Pharmacovigilance activity

4.1.1. Specific adverse reaction follow-up questionnaires

Targeted questionnaires were proposed by the MAHs to collect additional follow-up information for spontaneous reports of DKA cases. These should capture the following key information:

- Blood sugar level
- Risk factors
- SGLT2 dose and concomitant medication(s)
- Outcome

The questionnaires should be included in the RMP, implemented, and the results discussed in future PSURs.

4.1.2. Non-clinical and clinical studies

The MAHs should endeavour to clarify the mechanism behind SGLT2 inhibitors-induced DKA occurrence, taking into account the potential relevance of pharmacogenomic characteristics of the affected patients and the potential role of co-medication. The MAH of dapagliflozin- and empagliflozin-containing products have planned and ongoing mechanistic studies which are required to be included in the RMP as category 3 studies. Such mechanistic study should also be undertaken by the MAH of canagliflozin-containing products and included in the RMP as a category 3 study. A non-clinical mechanistic study protocol is required to be submitted by the MAH of canagliflozin-containing products for review by the PRAC, within 6 months of adoption of the CHMP opinion. New relevant mechanistic information should be reported in the next PSUR.

No new clinical studies with regard to DKA with atypical presentation are considered necessary at this point. However in new or ongoing clinical trials, MAHs should prospectively collect samples from (newly enrolled) subjects, in order to identify patterns of hormone derangement that could explain the mechanism of action in case subjects are later experiencing DKA. While accepting that this may not be possible retrospectively, the MAHs should explore the feasibility of prospective plasma hormone sampling (e.g. insulin, glucagon and incretin) in new or ongoing clinical trials. The MAH of dapagliflozin-containing products proposed to adjudicate reported DKA events in future clinical studies, which is supported.

4.1.3. Non-interventional studies

The MAH of canagliflozin-containing products plans to conduct a retrospective cohort study using four US databases in order to compare the incidence of DKA among new users of any SGLT2 inhibitors and various other AHAs including SU, DPP-4 inhibitors, GLP-1 agonists, thiazolidinediones, insulin, and other AHAs (combined as one group). The treatment groups will be matched using a propensity scoring method to control for confounding effects.

The MAH of dapagliflozin-containing products plans an epidemiological study assessing the incidence of DKA among new users of SGLT2 inhibitors and other classes of antidiabetic medication. Relevant information on the incidence of DKA occurring in T2DM patients on different antidiabetic therapies is expected from this study. It should however be acknowledged that the proposed study is not population based but based on a healthcare claims database which could bias the results. Another aspect that the MAH should consider to broaden the primary outcome of the study would be to include less specific diagnosis codes.

The MAH of empagliflozin-containing products has been required to perform, and is currently discussing with the FDA an enhanced pharmacovigilance study of spontaneous cases of ketoacidosis in patients treated with empagliflozin. The MAH also proposes to add DKA as a safety topic of interest in a category 3 PASS planned to assess a number of risks in patients treated with empagliflozin compared with patients treated with other SGLT2 inhibitors or with dipeptidyl peptidase-4 (DPP-4) inhibitors. The proposed amendment should be implemented.

The three studies should also be included in the RMPs as category 3 studies and MAHs are required to submit their protocols to the EMA for assessment by the PRAC, within 6 months of adoption of the CHMP opinion. In designing these protocols, it should be considered that different antidiabetic agents may have different propensities to cause ketoacidosis, therefore comparators for these PASS studies should be carefully chosen to allow accurate quantification of the risk attributable to SGLT2 inhibitors and minimise confounding. Similarly the potential for drug-drug interactions affecting the risk of ketoacidosis should be carefully considered in the study designs.

Finally ongoing or planned drug utilisation studies aiming to investigate off-label use of dapagliflozin in the EU in relation to specific criteria (including use in T1DM patients) and to assess the characteristics of patients initiating empagliflozin treatment (including potential off-label use) are expected to provide interesting information and should be included in the RMP as category 3 studies. The MAH are required to submit the final study reports to EMA as they become available. Similarly, as it cannot be assumed that the results of these studies could be extrapolated to canagliflozin-containing products, the MAH of these products is required to conduct a drug utilisation study, evaluating canagliflozin utilisation patterns, including off-label use in T1DM patients. A DUS protocol is required to be submitted by the MAH of canagliflozin-containing products for review by the PRAC, within 6 months of adoption of the CHMP opinion. The study should be included in the RMP as a category 3 and, ideally, be based on secondary observational data via existing databases. Off-label use should be discussed in the next PSURs.

4.2. Risk minimisation activities

4.2.1. Amendments to the product information (PI)

The PRAC considered that routine risk minimisation measures in the form of updates to the PI would be necessary in order to minimise the risk of DKA associated with the use of SGLT2 inhibitors. These changes include amendments to sections 4.4 and 4.8 the SmPC.

DKA was added as an adverse event with cross-reference to a warning included to inform physicians and patients of the possible occurrence of atypical DKA together with the symptoms and risk factors to consider and corresponding recommended actions.

The Package Leaflet was amended accordingly.

In addition, inconsistencies regarding actions to be taken in case of side effects related to lactic acidosis and hypoglycaemia in section 4 of the package leaflet of Xigduo were noted. The PRAC took the opportunity to correct these in this procedure.

4.2.2. Direct Healthcare Professional Communications

A DHPC was disseminated in June 2015 based on the information available, to increase awareness of healthcare professionals to the possible risk of DKA with atypical presentation. A DHPC with updated information further to this review was considered needed and the PRAC therefore adopted the wording of a Direct Healthcare Professional Communication to inform healthcare professionals of additional information identified during the review, including the risk factors and cases where the treatment should be temporarily or permanently discontinued. The PRAC also agreed on a communication plan.

5. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for SGLT2 inhibitors-containing medicinal products.
- The PRAC reviewed the totality of the data submitted by the marketing authorisation holders in relation to the risk of DKA in association with SGLT2 inhibitors-containing products and in support of the efficacy of SGLT2 inhibitors-containing products.
- The PRAC considered that the efficacy of these products had been adequately demonstrated in their currently authorised indications in monotherapy and in combination as an adjunct to diet and exercise to improve glycaemic control in T2DM adult patients.
- The PRAC concluded that a small excess risk of DKA associated with SGLT2 inhibitors treatment in patients with T2DM could not be excluded. Importantly, DKA with atypical presentation may occur in association with SGLT2 inhibitors.
- The PRAC therefore, was of the view that the risk of DKA should be minimised by its inclusion in the PI with a warning highlighting to healthcare professional and patients the possible atypical presentation of DKA to be considered in the occurrence of non-specific symptoms, together with the risk factors, and recommendations regarding treatment discontinuation.
- The PRAC further concluded that a risk of DKA, including with atypical presentation, is also associated with the use of SGLT2 inhibitors in patients with T1DM. This is not an approved indication for SGLT2 inhibitors containing products, nevertheless the PRAC considered that healthcare professionals should be warned of this risk and reminded that patients with T1DM should not be treated with SGLT2 inhibitors.

In view of the above, the Committee considers that the benefit-risk balance of SGLT2 inhibitors-containing products remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for SGLT2 inhibitors-containing products.

6. EPAR changes

The EPAR will be updated following Commission Decision for this procedure under Article 20 of Regulation (EC) No 726/2004. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

6.1. Scope

Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 10 June 2015 the opinion of the European Medicines Agency on the risk of diabetic ketoacidosis (DKA) in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors and requested the Agency to assess the impact thereof on the benefit-risk balance of canagliflozin-containing medicinal products (Invokana and Vokanamet), dapagliflozin-containing medicinal products (Forxiga and Xigduo), and empagliflozin-containing medicinal products (Jardiance and Synjardy) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

The notification for the procedure is appended to this recommendation.

6.2. Summary

Please refer to the assessment report:

SGLT2 inhibitors - EMEA/H/A-20/1419

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