NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

E-mail: ReferralNotifications@ema.europa.eu

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

Product Names Procedure name	INVOKANA (canagliflozin) VOKANAMET (canagliflozin / metformin) FORXIGA (dapagliflozin) XIGDUO (dapagliflozin / metformin) JARDIANCE (empagliflozin) SYNJARDY (empagliflozin / metformin) SGLT2 inhibitors and Diabetic Ketoacidosis
Active Substance(s)	Canagliflozin containing products, Dapagliflozin containing products, Empagliflozin containing products
Pharmaceutical form(s)	All
Strength(s)	All
Route of administration(s)	All
Marketing Authorisation Holders	AstraZeneca AB Boehringer Ingelheim Janssen- Cilag International

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. SGLT2 is expressed in the proximal renal tubules and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By blocking the action of SGLT2, SGLT2 inhibitors cause more glucose to be removed via the urine, thereby reducing the levels of glucose in the blood via an insulin-independent mechanism.

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. DKA most commonly occurs in patients with type 1 diabetes and is usually accompanied by high blood glucose levels (>250 mg/dl). DKA has been reported in a significant number of patients treated with SGLT2 inhibitors that had type 2 diabetes. In a number of cases atypical moderately increased glucose values or glucose values below 14 mmol/l (250 mg/dl) were reported, whereas hypoglycemia was reported in one case. DKA has also been reported in patients with type 1 diabetes treated with SGLT2 inhibitors which is not an approved indication.

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 on 19 May 2015 for the SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin (PTs: ketoacidosis, diabetic ketoacidosis, ketosis), leading to an identification of a safety signal.

The EV search retrieved ninety-six cases in association with canagliflozin all outside the EU. In 33 cases canagliflozin was used for type 1 diabetes ('off-label' use) and these cases were excluded from further analysis. In the remaining 63 cases the time-to-onset varied from 3 days up to 1 year (but in 1/3 cases reaction occurred within the first month of treatment). All cases were serious and 53 required hospitalisation. Forty-six distinct cases were retrieved from the EV search in association with dapagliflozin. Eighteen of these cases were from the EU and the remaining ones were reported in the rest of the world. In 12 cases dapagliflozin was used for type I diabetes ('off-label' use). In 20 cases the time-to-onset varied from 3 days up to 1 year (in 11 cases reaction occurred within the first 2 months of treatment). All cases were serious and 16 required hospitalisation. Five cases were retrieved in association with empagliflozin from outside the EU, including 3 cases reported with dehydration, vomiting or infection. The time-to-onset was 1 day, 6 days and 1.5 month, 2 cases had positive de-challenge and 2 cases were reported as related. One case was 'off label' use for the treatment of type 1 diabetes.
From the analysis of all cases for the three SGLT2 inhibitors mentioned above, the time-to-onset of DKA is suggestive of causal association with these active substances. Taking into account the severity of these reports and the general pattern seen across these medicinal products further investigation is required.

Moreover, the scientific evidence with regards to DKA is growing, including in the literature. Two articles were found that are relevant. The first article[1] describes a case of severe ketoacidosis associated with an SGLT2 inhibitor during a low-carbohydrate diet. The second article[2] describes a case of persistent glucosuria in the absence of hyperglycaemia 11 days after stopping canagliflozin.

In addition, according to the recent FDA warning, a search of the FDA Adverse Event Reporting System database identified 20 cases of acidosis reported as DKA, ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 to 6 June 2014. All patients required emergency room visits or hospitalisation to treat the ketoacidosis.

In conclusion, serious and sometimes life-threatening cases of DKA have been reported in patients on SGLT2 inhibitor treatment (canagliflozin, dapagliflozin or empagliflozin) for type 2 diabetes. 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 type 2 diabetes could delay diagnosis and treatment. Cases of DKA were also reported in patients on SGLT2 inhibitors for type 1 diabetes, which is not an approved indication.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance for these medicinal products. The EC requests the EMA to give its opinion by 31 May 2016 on whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

As the request is based on the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

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

[redacted]

Sabine Jülicher
Head of Unit
European Commission
DG Health and Food Safety
Unit D5 - Medicinal products – authorisations, European Medicines Agency

10/6/2015

[1] Tomohide Hayami et al. Case of ketoacidosis by a sodium-glucose co-transporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Invest, 2015 doi: 10.1111/jdi.12330

[2] Kelsey Burr et al. A Case Report of Ketoacidosis Associated with Canagliflozin (Invokana). SAT 586 -604-Diabetes Case Reports II, Clinical. The Endocrine Society's 97th Annual meeting and Expo, 2015