

**Annex IV**  
**Scientific conclusions**

## Scientific conclusions

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, 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, 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, often life-threatening condition, which usually develops in diabetic patients 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 1,000 patient-years.

A search in Eudravigilance (EV) database was performed by the EMA on 19 May 2015 for the three SGLT2 inhibitors. One hundred and two 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. 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. Forty-six cases of DKA were also reported in patients on SGLT2 inhibitors for T1DM, which is not currently an approved indication for these products. A safety warning on DKA was issued by the FDA for this therapeutic class in the same month. Taking into account the severity of these cases and the general pattern seen across these medicinal products, the European Commission requested, on the 10 of June 2015 and pursuant to Article 20 of Regulation No 726/2004, the opinion of the Agency on whether the marketing authorisation of canagliflozin-, dapagliflozin- and empagliflozin-containing medicinal products, should be maintained, varied, suspended or revoked.

### Overall summary of the scientific evaluation by the PRAC

When considering all the data submitted by the MAHs from clinical and non-clinical studies, post-marketing reports and in published literature, in relation to the risk of diabetic ketoacidosis (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 SGLT2 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 product information 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. 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. 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, including with atypical presentation, is also 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. The 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. The RMP of all these products should be updated accordingly.

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 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.

### **Grounds for PRAC 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 product information 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 PRAC considered that the benefit-risk balance of Forxiga, XigDuo, Invokana, Vokanamet, Jardiance and Synjardy remains favourable subject to the agreed amendments to the product information.

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

### **CHMP opinion**

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.