HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

SGLT2 inhibitors – Reminder of the associated risk of diabetic ketoacidosis (DKA)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors* are indicated in adults for the treatment of Type 2 diabetes (T2DM), as monotherapy or in combination with other diabetes medicines.

Diabetic ketoacidosis (DKA)

Rare cases of diabetic ketoacidosis (DKA), including atypical cases with only moderately increased glucose values (below 14mmol/L (250mg/dl)), have been reported in patients taking SGLT2 inhibitors. An atypical presentation of DKA, with only moderately increased blood glucose levels, has the potential to delay diagnosis and treatment of this condition in patients. Patients should be informed of the non-specific signs and symptoms of DKA and advised to seek medical attention immediately if any of the following are experienced: anorexia, nausea and vomiting, abdominal pain, excessive thirst, difficulty breathing, unusual fatigue or sleepiness, confusion, sweet smelling breath, metallic taste in mouth, or different odour to urine or sweat. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where a diagnosis of DKA is suspected or diagnosed, treatment with SGLT2 inhibitors should be discontinued immediately. Treatment with SGLT2 inhibitors should not be restarted in patients who experienced DKA during use, unless another clear precipitating factor for DKA is identified and resolved.

Risk factors for development of DKA

Before initiating SGLT2 inhibitors factors in the patient history that may predispose to ketoacidosis should be considered. SGLT2 inhibitors should be used with caution in patients at higher risk of DKA, including patients with a low beta-cell function reserve (e.g. T2DM patients with low C-peptide or latent autoimmune diabetes in adults (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 or missed and patients with increased insulin requirements due to acute medical illness, infections, surgery or alcohol abuse.

In addition, treatment with SGLT2 inhibitors should be interrupted in patients hospitalised for major surgical procedures or acute serious medical illnesses due to an increased risk of DKA in these patients. Following interruption of SGLT2 inhibitor treatment in these patients, monitoring of ketones is recommended. There is evidence that SGLT2 inhibitors may diminish the excretion of ketone bodies in the urine, thereby making urine measurement of ketone bodies less reliable compared to blood testing. Therefore, measurement of blood ketone levels is preferred to urine. SGLT2 inhibitor treatment may be restarted when ketone values are normal, and the patient's condition has stabilised.

Reminder of removal of Type 1 Diabetes Mellitus indication from Forxiga 5mg (dapagliflozin)

In October 2021, the product information** for the SGLT2 inhibitor dapagliflozin 5mg, was updated to remove the treatment of Type 1 diabetes (T1DM) as an indication. Prior to this, dapagliflozin had been the only inhibitor that was licensed for treatment of T1DM. In studies where dapagliflozin was used in patients with T1DM, DKA was reported with a 'common' frequency (i.e. occurring in at least 1 per 100 patients). Dapagliflozin remains authorised in adults for the treatment of T2DM, the treatment of symptomatic chronic heart failure with reduced ejection fraction, and the treatment of chronic kidney disease. Discontinuation of dapagliflozin in patients with T1DM must be made by, or in consultation with, a physician specialised in diabetes care and be conducted as soon as clinically practical. After stopping dapagliflozin treatment in patients with T1DM, frequent blood glucose monitoring is recommended, and the insulin dose should be increased carefully to minimise the risk of hypoglycaemia.

Key Message

- Rare but serious and sometimes life-threatening and fatal cases of diabetic ketoacidosis (DKA) have been reported in patients taking SGLT2 inhibitors for the treatment of T2DM. In a number of the reports, the presentation of the condition was atypical, with only moderately increased glucose values (below 14mmol/L (250mg/dl)).
- SGLT2 inhibitors should only be used in the treatment of T2DM. The previously existing indication for T1DM for dapagliflozin 5mg was removed in October 2021.
- Patients should be assessed for ketoacidosis immediately if symptoms of DKA occur, regardless of blood glucose level.
- Cases of DKA have been reported in patients using SGLT2 inhibitors undergoing surgical procedures. SGLT2 treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses.
- Ketone bodies should be monitored in these patients, preferably by measurement of blood ketone levels. Treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.
- Suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie/report).

**SGLT2 inhibitor-containing products include Ebymect, Edistride, Forxiga, Glyxambi, Invokana, Jardiance, Qtern, Synjardy, Segluromet, Steglatro, Steglujan, Xigduo, and Vokanamet. Further details are available on www.hpra.ie and www.ema.europa.eu.*
***The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie and www.ema.eurpa.eu.*