28/04/2016
EMA/265224/2016

EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes

Healthcare professionals should be aware of possible atypical cases

On 25 February 2016, the European Medicines Agency (EMA) confirmed recommendations[1] to minimise the risk of diabetic ketoacidosis in patients taking SGLT2 inhibitors (a class of type 2 diabetes medicines).

Diabetic ketoacidosis is a serious complication of diabetes caused by low insulin levels. Rare cases of this condition, including life-threatening ones, have occurred in patients taking SGLT2 inhibitors for type 2 diabetes and a number of these cases have been atypical, with patients not having blood sugar levels as high as expected.

An atypical presentation of diabetic ketoacidosis can delay diagnosis and treatment. Healthcare professionals should therefore consider the possibility of ketoacidosis in patients taking SGLT2 inhibitors who have symptoms consistent with the condition even if blood sugar levels are not high.

Following a review of the cases, EMA recommended updating the product information of SGLT2 inhibitors to list diabetic ketoacidosis as a rare adverse reaction (affecting up to 1 in 1,000 patients).

Patients taking these medicines should be aware of the symptoms of diabetic ketoacidosis, including rapid weight loss, nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat. Patients should contact a doctor or the nearest hospital straightaway if they have any of these symptoms.

If diabetic ketoacidosis is suspected or confirmed, treatment with SGLT2 inhibitors should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.

Healthcare professionals should exercise caution with SGLT2 inhibitors in patients with risk factors for ketoacidosis and inform patients of these factors. These include low insulin-producing capacity in the pancreas, a sudden drop in a patient's insulin dose, increased insulin requirement (due to illness, surgery or alcohol abuse) or conditions that can restrict food intake or lead to severe dehydration.

In addition, EMA recommended temporarily stopping SGLT2 inhibitors in patients who are undergoing major surgery or are in hospital due to serious illness.

[1] PRAC recommendations issued on 11 February 2016

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Finally, EMA reminded healthcare professionals that SGLT2 inhibitors are not authorised for type 1 diabetes, noting that cases of ketoacidosis have also occurred during off-label use and clinical trials in type 1 diabetes.

The benefits of these medicines continue to outweigh the risks in the treatment of type 2 diabetes.

EMA's recommendations are based on an initial review by its Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), which confirmed them and adopted the Agency's final opinion.

The CHMP opinion was then sent to the European Commission, which issued a legally-binding decision valid throughout the EU.

Information for patients

- Rare cases of diabetic ketoacidosis have occurred in people with type 2 diabetes taking diabetes medicines known as SGLT2 inhibitors.
- Diabetic ketoacidosis is a serious complication of diabetes. Symptoms include rapid weight loss, nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.
- Some of the cases of diabetic ketoacidosis in people taking SGLT2 inhibitors did not show the very high sugar levels normally associated with this condition.
- If you have any of the symptoms above while taking an SGLT2 inhibitor, contact a doctor or the nearest hospital straightaway even if your sugar level is not particularly high. You may need emergency treatment and your diabetes medicine may need to be changed.
- SGLT2 inhibitors in the EU are available under the following trade names: Ebymect, Edistride, Forxiga, Invokana, Jardiance, Synjardy, Vokanamet and Xigduo.

Information for healthcare professionals

- Rare cases of diabetic ketoacidosis, including life-threatening ones, have occurred in patients taking SGLT2 inhibitors, used to treat type 2 diabetes. A number of these cases were atypical with patients having only moderately raised blood sugar levels and some of them occurred during off-label use and clinical trials in patients with type 1 diabetes.
- Always consider the possibility of diabetic ketoacidosis in patients taking SGLT2 inhibitors who have non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.
- Inform patients of the signs and symptoms of diabetic ketoacidosis and advise them to seek medical advice immediately if they develop such signs and symptoms.
- Stop treatment with SGLT2 inhibitors immediately if diabetic ketoacidosis is suspected or confirmed, and do not re-start treatment unless another clear precipitating factor for the condition is identified and resolved.
- Stop treatment with SGLT2 inhibitors temporarily in patients undergoing major surgical procedures or hospitalised due to acute serious medical illnesses. Treatment may be restarted once the patient's condition has stabilised.

- Exercise caution in patients with risk factors for ketoacidosis and inform patients of these factors. These include low reserve of insulin-secreting cells, a sudden reduction in insulin dose, an increased requirement for insulin (due to illness, surgery or alcohol abuse) and conditions that restrict food intake or can lead to severe dehydration.
- Healthcare professionals are reminded that SGLT2 inhibitors are only authorised for treating type 2 diabetes.

More about the medicine

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are medicines used to treat type 2 diabetes. They block a protein in the kidneys called SGLT2, which absorbs glucose back from the urine into the bloodstream as the blood is filtered in the kidneys. By blocking the action of SGLT2, these medicines cause more glucose to be removed through the urine, thereby reducing the levels of glucose in the blood.

The following SGLT2 inhibitors are authorised in the EU: Ebymect (dapagliflozin/metformin), Edistride (dapagliflozin), Forxiga (dapagliflozin), Invokana (canagliflozin), Jardiance (empagliflozin), Synjardy (empagliflozin / metformin), Vokanamet (canagliflozin / metformin) and Xigduo (dapagliflozin / metformin).

More about the procedure

The review of SGLT2 inhibitors was initiated at the request of European Commission in June 2015, under Article 20 of Regulation (EC) No 726/2004.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's final opinion.

The CHMP opinion was forwarded to the European Commission, which issued a final legally binding decision applicable in all EU Member States on 25/04/2016 (Invokana, Jardiance) and 28/04/2016 (Forxiga, XigDuo, Synjardy, Vokanamet).

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