

14<sup>th</sup> March 2016

## **Direct Healthcare Professional Communication**

### **Updated advice on the risk of diabetic ketoacidosis during treatment with SGLT2 inhibitors**

**(INVOKANA ▼ (canagliflozin), VOKANAMET ▼ (canagliflozin / metformin), FORXIGA ▼ (dapagliflozin), XIGDUO ▼ (dapagliflozin / metformin), JARDIANCE ▼ \* (empagliflozin), SYNJARDY ▼ \* (empagliflozin / metformin))**

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and Health Products Regulatory Authority (HPRA), Janssen-Cilag Limited, AstraZeneca Limited and Boehringer Ingelheim Limited would like to inform you of the latest recommendations regarding the risk of diabetic ketoacidosis (DKA) during treatment with SGLT2 inhibitors (canagliflozin, dapagliflozin or empagliflozin). This follows on the outcome of an evaluation by the EMA of the risk of diabetic ketoacidosis during treatment with SGLT2 inhibitors.

Rare but serious, sometimes life-threatening and fatal cases of diabetic ketoacidosis have been reported in patients on SGLT2 inhibitor treatment 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. Such atypical presentation of diabetic ketoacidosis in patients with diabetes could delay diagnosis and treatment.

#### ***Summary of updated advice***

- The risk of diabetic ketoacidosis 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. Prescribers should inform patients of signs and symptoms of metabolic acidosis and advise them to immediately seek medical advice if they develop such signs and symptoms.
- In patients where DKA is suspected or diagnosed, treatment with SGLT2 inhibitors should be discontinued immediately.
- Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.
- Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with SGLT2 inhibitors may be restarted once the patient's condition has stabilised.

The information for the healthcare professionals in the summary of product characteristics (SmPC) and the information for patients in the package leaflet will be updated accordingly.

### **Further information on the safety concern and the recommendations**

The majority of patients treated with SGLT2 inhibitors who developed diabetic ketoacidosis required hospitalisation. To date, many of them have occurred during the first 2 months of treatment. In some cases, just before or at the same time as the ketoacidosis occurred, patients experienced dehydration, low food intake, weight loss, infection, surgery, vomiting, a decrease in their insulin dose or poor control of diabetes. In a number of cases atypical moderately increased glucose values or glucose values below 14 mmol/l (250 mg/dl) were reported, whereas hypoglycaemia was reported in one case. There were also cases of ketoacidosis shortly after discontinuation of SGLT2 inhibitors.

The underlying mechanism for SGLT2 inhibitor-associated diabetic ketoacidosis is not established. Diabetic ketoacidosis usually develops when insulin levels are too low. Diabetic ketoacidosis occurs most commonly in patients with type 1 diabetes and is usually accompanied by high blood glucose levels (>14 mmol/l). However, the cases referred to above concern patients with type 2 diabetes and in a number of cases blood glucose levels were only slightly increased, in contrast to typical cases of diabetic ketoacidosis.

#### Further recommendations:

Before initiating treatment with SGLT2 inhibitors, factors in the patient history that may predispose to ketoacidosis should be considered. These factors include:

- a low beta-cell function reserve (e.g. Type 2 diabetes patients with low C-peptide, latent autoimmune disease in adults (LADA) or patients with a history of pancreatitis),
- conditions that lead to restricted food intake or severe dehydration,
- sudden reduction in insulin,
- increased insulin requirements due to acute medical illness,
- surgery,
- alcohol abuse.

SGLT2 inhibitors should be used with caution in these patients. In addition, patients should be informed of the above risk factors.

A substantial proportion of the cases concerned off-label use in patients with type 1 diabetes. Prescribers are reminded that type 1 diabetes is not an approved indication for SGLT2 inhibitors. Based on limited clinical data, ketoacidosis appears to occur with common frequency in patients with type 1 diabetes.

## ***Call for reporting***

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with these products in accordance with the national spontaneous reporting system.

Suspected adverse reactions should be reported to the Health Products Regulatory Authority, using a Yellow Card obtained either from the HPRA, or electronically via the website at [www.hpra.ie](http://www.hpra.ie).

Adverse reactions can also be reported to the HPRA by calling (01) 676 4971.

▼ These medicinal products are subject to additional monitoring to support risk management and it is therefore important to report any suspected adverse events.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Suspected adverse reactions should also be reported to the relevant Marketing Authorisation Holder (MAH) (see contact details below).

<b>Marketing Authorisation Holder</b>	<b>Product Names</b>	<b>Email address for adverse reaction reporting</b>	<b>Phone</b>	<b>Fax</b>
AstraZeneca UK Limited	FORXIGA (dapagliflozin), XIGDUO (dapagliflozin / metformin),	Medical.informationUK@astrazeneca.com	1800 800 899	0044 (0)1582 838 003
Boehringer Ingelheim Limited	JARDIANCE (empagliflozin), SYNJARDY (empagliflozin / metformin)	PV_local_UK_ireland@boehringer- ingelheim.com	0044 (0)1344 741346	+44 1344 742661
Janssen-Cilag International N.V.	INVOKANA (canagliflozin), VOKANAMET (canagliflozin / metformin)	dsafety@its.jnj.com	0044 (0)1494 567447	0044 (0)1494 567799

## ***Company contact points***

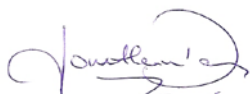
If you have further questions or require additional information, please contact:

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Yours faithfully,



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