09 July 2015

Direct Healthcare Professional Communication

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 the Medicines and Healthcare products Regulatory Agency (MHRA), Janssen-Cilag Limited, AstraZeneca Ltd and Boehringer Ingelheim Ltd would like to inform you of the following:

Summary

- Serious, sometimes life-threatening cases of diabetic ketoacidosis 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. Such atypical presentation of diabetic ketoacidosis in patients with diabetes could delay diagnosis and treatment.
- Patients on SGLT2 inhibitors should be tested for ketones when they present with symptoms of acidosis in order to prevent delayed diagnosis and patient management.
- Cases of diabetic ketoacidosis were also reported in patients with type 1 diabetes who were given SGLT2 inhibitors. Prescribers are reminded that type 1 diabetes is **not** an approved indication for this drug class.

Further information on the safety concern and the recommendations

Serious and sometimes life-threatening cases of diabetic ketoacidosis in patients under treatment with SGLT2-inhibitors (canagliflozin, dapagliflozin and empagliflozin) have been reported, the majority of them requiring hospitalisation. Up to half of the cases occurred during the first two months of treatment. One third of the cases concerned off-label use in patients with type 1 diabetes. 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 hypoglycemia was reported in one case. There were also cases of ketoacidosis shortly after discontinuation of SGLT2 inhibitors.

*JARDIANCE and SYNJARDY are co-promoted by Boehringer Ingelheim Limited and Eli Lilly and Company Limited

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, in a number of cases described above blood glucose levels were only slightly increased, in contrast to typical cases of diabetic ketoacidosis.

Prescribers should inform patients of the signs and symptoms of metabolic acidosis (such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue and sleepiness) and advise them to immediately seek medical advice if they develop such signs and symptoms.

It is recommended that patients taking SGLT2 inhibitors should be assessed for ketoacidosis when they present with signs or symptoms of metabolic acidosis in order to prevent delayed diagnosis and patient management. If ketoacidosis is suspected, treatment with SGLT2 inhibitors should be discontinued. If ketoacidosis is confirmed, appropriate measures should be taken to correct the ketoacidosis and to monitor glucose levels.

The EMA is further investigating the risk of diabetic ketoacidosis with SGLT2 inhibitors. Any new advice will be communicated promptly.

For further information please refer to the Summaries of Product Characteristics / Patient information Leaflets and see relevant contact details for individual companies below.

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.

Please continue to report any suspected adverse drug reactions to the MHRA through the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

Alternatively, prepaid Yellow Cards for reporting are available:
upon request by mail: “FREEPOST YELLOW CARD”
at the back of the British National Formulary (BNF)
by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
or by electronic download through the Yellow Card section of the MHRA website

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 (see contact details below).

Marketing Authorisation Holder	Product Names	Email address for adverse reaction reporting	Phone	Fax
AstraZeneca UK Limited	FORXIGA (dapagliflozin), XIGDUO (dapagliflozin / metformin),	Medical.informationUK@astrazeneca.com	01582 836836	01582 838003
Boehringer Ingelheim Limited	JARDIANCE (empagliflozin), SYNJARDY (empagliflozin / metformin)	PV_local_UK_ireland@boehringer-ingelheim.com	0800 328 1627	0800 328 1628
Janssen-Cilag International N.V.	INVOKANA (canagliflozin), VOKANAMET (canagliflozin / metformin)	dsafety@its.jnj.com	01494 567447	01494 567799

Company contact point

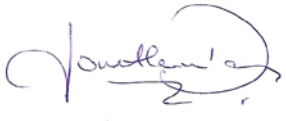
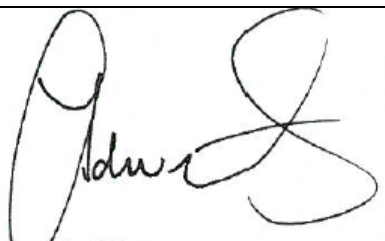
If you have further questions or require additional information, please contact:

AstraZeneca Medical Information Department:
Email: Medical.informationUK@astrazeneca.com
Telephone: 01582 836836

Boehringer Ingelheim Medical Information Department:
Email: medinfo.bra@boehringer-ingelheim.com
Telephone: 01344 742579

Janssen-Cilag Ltd Medical Information Department
Email: medinfo@janssen-cilag.co.uk
Telephone : 0800 731 8450 or 01494 567 567

Yours faithfully,

		
Jonathan Day Medical & Healthcare Affairs Director AstraZeneca UK	Charles de Wet Medical Director Boehringer Ingelheim UK and Ireland	Rozlyn Bekker Medical Director Janssen UK and Ireland