DHPC agreed by CHMP on 25 June 2015

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 Health Products Regulatory Authority (HPRA), 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 them occurred during the first 2 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 hypoglycaemia 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 Ireland Limited and Eli Lilly and Company (Ireland) 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.

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. 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).

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	1800 800 899	0044 (0)1582 838 003
Boehringer Ingelheim Limited	JARDIANCE (empagliflozin), SYNJARDY (empagliflozin / metformin)	PV_local_UK_ireland@boehringer-ingelheim.com	01 2913960	+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 point

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

AstraZeneca Medical Information Department:
Email: Medical.informationUK@astrazeneca.com
Telephone: 1800 800 899

Boehringer Ingelheim Medical Information Department:
Email: medinfo.bra@boehringer-ingelheim.com
Telephone: +44 1344 742579

Janssen-Cilag Ltd Medical Information Department
Email: medinfo@janssen-cilag.co.uk
Telephone: +353 1 800 709 122

Yours faithfully,

David Morrow
Head of Medical
AstraZeneca Ireland

Charles de Wet
Medical Director
Boehringer Ingelheim UK and Ireland

Dr Michelle de Brun
MBBChBAO, AFRCSI, MICGP, DCH
Head of Medical Affairs
Janssen Ireland