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)

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Dear **HCP**,

In agreement with the European Medicines Agency (EMA) and the Medicines Authority, *AstraZenica AB, Boehringer Ingelheim and Janssen-Cilag International N.V.* 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 hospitalization. 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 hypoglycemia 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, 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 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.

Call for reporting
Any suspected adverse reactions and medication errors can be reported to the Medicines Authority or to the license holders of SGLT-2 containing products. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Company contact points
Contact point details for further information and ADR reporting are given in the product information of the medicine (SmPC and Package Leaflet).

Yours sincerely,

Post Licensing Directorate
Medicines Authority

Disclaimer
This Direct Healthcare Professional Communication has been submitted to you on behalf of *AstraZenica, AB, Boehringer Ingelheim and Janssen-Cilag International N.V.*