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Direct Healthcare Professional Communication: Risk of Diabetic Ketoacidosis during Treatment with Sodium Glucose Co-transporter 2 Inhibitors

9th July 2015

Dear Healthcare Professional:

The purpose of this letter is to inform you of new safety information for prescription medicines containing canagliflozin, dapagliflozin, or empagliflozin, which are inhibitors of sodium glucose co-transporter 2 (SGLT2) approved as oral antihyperglycemic agents for the treatment of patients with type 2 diabetes.

Summary

- Serious and sometimes life-threatening cases of diabetic ketoacidosis (DKA) 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 DKA 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 DKA 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

Description of the Issue

DKA occurs most commonly in patients with type 1 diabetes, although it can occur less commonly in type 2 diabetes, and is usually accompanied by high blood glucose levels (>14 mmol/L [250 mg/dL]).

Serious and sometimes life-threatening cases of DKA in patients treated with SGLT2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) have been reported, the majority of them requiring hospitalization. Of the limited number of cases reported, some involved 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 acute illness (eg, urinary tract infection, urosepsis, gastroenteritis, influenza, or

trauma), reduced caloric or fluid intake, and reduced insulin dose. The underlying mechanism for SGLT2 inhibitor-associated diabetic ketoacidosis is not established.

The presentation of DKA was sometimes atypical in that glucose levels were only mildly elevated at less than 11 mmol/L (200 mg/dL), while DKA typically occurs at glucose levels greater than 14 mmol/L (250 mg/dL).

Recommendations for Healthcare Professionals:
SGLT2 inhibitors should be used according to the TGA approved Australian Product Information. 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, or sleepiness) and advise them to immediately seek medical advice if they develop any 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.

Products Affected

- INVOKANA® (canagliflozin) Tablets 100mg (AUST R 200184) and 300mg (AUST R 200180)
- FORXIGA® (dapagliflozin) Tablets 10mg (AUST R 180147) and XIGDUO® XR (dapagliflozin and metformin hydrochloride XR) Tablets 5mg/1000mg (AUST R 211296), 10mg/1000mg (AUST R 211295) and 10mg/500mg (AUST R 211294).
- JARDIANCE® (empagliflozin) Tablets 10mg (AUST R 208829) and 25mg (AUST R 208827).

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 events should be reported using the TGA Report a Problem web page http://www.tga.gov.au/reporting-problems

Company Contact Points

The Sponsors of SGLT2 inhibitors are committed to monitoring the safety of our products. We encourage healthcare professionals to report any suspected adverse events for **INVOKANA**, **FORXIGA**, **XIGDUO XR** or **JARDIANCE** to the TGA (at http://www.tga.gov.au/safety/problem-medicine.htm) and/or to the following contacts:-

AstraZeneca: - If you have further questions relating to **FORXIGA or XIGDUO XR**, please contact AstraZeneca Medical Information on 1800 805 342 or medinfo.australia@astrazeneca.com.

Boehringer Ingelheim: - If you have further questions relating to **JARDIANCE**, please contact Boehringer Ingelheim Medical Information on 1800 226 315 or medinfo.au@boehringer-ingelheim.com.

Janssen-Cilag: - If you have further questions relating to INVOKANA, please contact Janssen Medical Information on 1800 226 334 or medinfo@janau.jnj.com.

For copies of the full Product Information documents for any of the affected products please refer to the TGA website: http://www.tga.gov.au or contact the sponsor of the product as per the details above.

PLEASE DISTRIBUTE TO OTHER HEALTH CARE PROVIDERS IN YOUR SURGERY

Yours Sincerely

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