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

July 10, 2015

Audience : Specialists in internal medicine/diabetologists/endocrinologists, general or family practitioners, emergency healthcare professionals, hospitalists and critical care physicians, diabetes nurses, advanced nurse practitioners, physician assistants, and certified diabetes educators

Dear Health Care Professional:

On June 22, 2015, Health Canada issued an advisory entitled "Information Update - Forxiga, Invokana: Health Canada begins safety review of diabetes drugs known as SGLT2 inhibitors and risk of ketoacidosis" which can be accessed at the following link: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/forxiga-invokana-eng.php

Consistent with this advisory and to ensure effective distribution of this information, Janssen Inc. and AstraZeneca Canada Inc. have collaborated and are proactively issuing a Healthcare Professional Communication to inform you of new safety information for prescription medicines containing canagliflozin and dapagliflozin, which are inhibitors of 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 or dapagliflozin) 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 or dapagliflozin) 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 Health Care Professionals:

SGLT2 inhibitors should be used according to the relevant prescribing information or summary of product characteristics. 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
- FORXIGA® (dapagliflozin) Tablets

For full prescribing information consult the Product Monographs as follows:

FORXIGA®: http://www.azinfo.ca/forxiga/pm367

INVOKANA™: http://www.janssen.ca/product/604

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.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax

Company Contact Points

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

Contact information for manufacturer of INVOKANA™
Medical Information Department
Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
Or call toll free at 1-800-567-3331

Contact information for manufacturer of FORXIGA®
AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, Ontario
L4Y 1M4
Or call toll free at 1-800-668-6000

Sincerely,

Original signed by

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