Important Safety Information on SGLT2 Inhibitors [INVOKANA® (canagliflozin), FORXIGA® (dapagliflozin), XIGDUO® (dapagliflozin/metformin), JARDIANCE™ (empagliflozin)] and the Risk of Diabetic Ketoacidosis

2016/05/16

Audience

Healthcare professionals including internal medicine specialists, endocrinologists, cardiologists, nephrologists, general or family practitioners, emergency healthcare professionals, critical care physicians, certified diabetes educators and pharmacists.

Key messages

- **Serious, sometimes life-threatening and fatal cases of diabetic ketoacidosis (DKA) have been reported in patients on sodium glucose co-transporter 2 (SGLT2) inhibitors for type 1 and type 2 diabetes.**
- **In a number of these cases, the presentation of the condition was atypical with only moderately increased blood glucose levels observed.**
- **SGLT2 inhibitors are NOT indicated for treatment of type 1 diabetes mellitus and should not be used in type 1 diabetes.**
- **It is recommended that:**
  - **if DKA is suspected or diagnosed, treatment with SGLT2 inhibitors should be discontinued immediately.**
  - **SGLT2 inhibitors should not be used in patients with a history of DKA.**
  - **in clinical situations known to predispose to ketoacidosis (e.g. major surgical procedures, serious infections and acute serious illness), consideration be given to temporarily discontinuing SGLT2 inhibitor therapy.**
  - **patients be informed of the signs and symptoms of DKA and be advised to immediately seek medical attention if they develop them.**
  - **caution be used before initiating SGLT2 inhibitor treatment in patients with risk factors for DKA.**
- **The Canadian Product Monographs of these products will be updated to reflect this safety information.**

What is the issue?
Clinical trial and post-market cases of DKA, a serious, life-threatening condition requiring urgent hospitalization have been reported in patients with type 1 and type 2 diabetes mellitus on SGLT2 inhibitor treatment.

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.

Products affected

Brand Name	Medicinal Ingredients	Manufacturer
INVOKANA®	canagliflozin	Janssen Inc.
FORXIGA®	dapagliflozin	AstraZeneca Canada Inc.
XIGDUO®	dapagliflozin and metformin	AstraZeneca Canada Inc.
JARDIANCE™	empagliflozin	Boehringer Ingelheim (Canada) Ltd.

Background information
Sodium glucose co-transporter type 2 (SGLT2) inhibitors are a class of drugs indicated as oral antihyperglycemic agents for the treatment of patients with type 2 diabetes.

The underlying mechanism for SGLT2 inhibitor-associated ketoacidosis is not clearly established. DKA usually develops when insulin levels are too low to prevent ketoacid accumulation. DKA occurs most commonly in patients with type 1 diabetes and is usually accompanied by high blood glucose levels (>14 mmol/L). However, the cases referred to above also concern patients with type 2 diabetes and in a number of cases blood glucose levels were only slightly increased, in contrast to typical cases of DKA.

The majority of the patients described in the above reports required hospitalization. To date, many of them have occurred during the first 2 months of treatment. In many 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.

A substantial proportion of the cases concerned use of SGLT2 inhibitors in patients with type 1 diabetes. SGLT2 inhibitors are **NOT** indicated for treatment of type 1 diabetes mellitus.

Information for consumers
Diabetic ketoacidosis (DKA) is a serious complication of diabetes caused by low insulin levels. Rare cases of this condition, including life-threatening and fatal ones, have occurred in patients taking SGLT2 inhibitors [INVOKANA® (canagliflozin), FORXIGA® (dapagliflozin), XIGDUO® (dapagliflozin/metformin), JARDIANCE™ (empagliflozin)] for type 1 and type 2 diabetes.

A number of these cases have been unusual, with patients having blood sugar levels that are not as high as typically expected in DKA, which can lead to a delay in diagnosis and treatment.

Patients taking any of these medicines should be aware of the symptoms of DKA, including loss of appetite, nausea or vomiting, stomach pain, feeling very thirsty, rapid breathing, confusion, feeling unusual tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.

Patients should immediately seek medical advice if they develop any of these symptoms. Patients should also inform their healthcare professional about medical issues or factors (see below) that may predispose them to ketoacidosis.

SGLT2 inhibitors are NOT indicated for treatment of type 1 diabetes mellitus and should not be used in type 1 diabetes.

Information for health care professionals

Before initiating treatment with SGLT2 inhibitors, factors in the patient history that may predispose to ketoacidosis should be considered. These factors include:

- patients on a very low carbohydrate diet (as the combination may further increase ketone body production),
- an acute serious illness,
- pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery),
- sudden insulin dose reduction (including insulin pump failure),
- alcohol abuse,
- conditions that lead to severe dehydration,
- hospitalization for major surgery or serious medical illness.

SGLT2 inhibitors should be used with caution in these patients. In addition, patients should be informed of these risk factors.

SGLT2 inhibitors should not be used in patients with a history of DKA.

A substantial proportion of the cases concerned off-label use in patients with type 1 diabetes. Prescribers are reminded that type 1 diabetes is **NOT** an approved indication for SGLT2 inhibitors.

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. If ketoacidosis is suspected, treatment with SGLT2 inhibitors should be discontinued.

Prescribers should inform patients of signs and symptoms of metabolic acidosis and advise them to immediately seek medical advice if they develop such signs and symptoms.

Action taken by Health Canada
This communication is a follow-up to an Information Update published by Health Canada on June 22, 2015 (www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/53892a-eng.php). Health Canada is currently working with the manufacturers to update the Canadian Product Monograph to reflect this safety information.

Report health or safety concerns
Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any adverse event or other serious or unexpected side effects to SGLT2 inhibitors should be reported to the appropriate manufacturer (see "Products affected") or to Health Canada.

Janssen Inc.
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Toronto, ON, M3C 1L9
Tel: 1-866-825-7122
www.janssen.com/canada

Boehringer Ingelheim (Canada) Ltd.
5180 South Service Rd.
Burlington, ON, L7L 5H4
Tel: 1 (800) 263-5103 Ext. 87233
Email: PV_local_Canada@boehringer-ingelheim.com

AstraZeneca Canada Inc.
1004 Middlegate Road
Mississauga, ON, L4Y 1M4
Tel: 1-800-668-6000
Email: medinfo.canada@astrazeneca.com

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.

For other health product inquiries related to this communication, contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,

Original signed by

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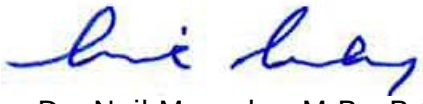
Vice President, Regulatory Affairs and Quality Management
Janssen Inc.



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