Summary Safety Review - Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors (canagliflozin, dapagliflozin, empagliflozin) - Assessing the Potential Risks of Prolonged or Incident Diabetic Ketoacidosis Despite Stopping Treatment in Adult Patients with Type 2 Diabetes

Product: Sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin-, dapagliflozin-, empagliflozin-containing products)

Potential Safety Issue: Prolonged (lasting 3 days or more) or incident (a new event) diabetic ketoacidosis (DKA), a serious condition where there are high levels of ketones (acids) in the blood, despite stopping treatment in adult patients with type 2 diabetes

Key Messages

- **Health Canada reviewed the following potential risks with SGLT2 inhibitors used in adult patients with type 2 diabetes:**
    - **prolonged DKA despite stopping SGLT2 inhibitor treatment as part of standard DKA management**
    - **incident DKA after surgery despite temporarily stopping treatment (temporary treatment cessation) prior to surgical procedures**
- **Health Canada's safety review could not rule out a possible drug class effect for the risk of prolonged DKA despite stopping SGLT2 inhibitor treatment as part of standard DKA management in adult patients with type 2 diabetes. Health Canada's review also identified a number of cases of incident DKA following surgery where treatment was temporarily stopped 2 days or less before surgery.**
- **To reduce the potential risk of incident DKA, Health Canada recommends stopping treatment with SGLT2 inhibitors at least 3 days before surgery or other invasive procedures requiring prolonged fasting.**
- **Health Canada is working with the manufacturers to update and align the Canadian product monograph (CPM) for SGLT2 inhibitors to include a warning about the risk of prolonged DKA despite stopping treatment as part of standard DKA management in adult patients with type 2 diabetes, and a recommendation for temporary treatment cessation before a surgical procedure. Health Canada will also inform healthcare professionals about these updates through a Health Product InfoWatch communication.**

Overview

Diabetic ketoacidosis is a serious and potentially life-threatening complication of diabetes that develops when the body breaks down fat for energy, which causes a buildup of ketones in the blood. Increased blood levels of ketones can lead to symptoms such as difficulties in breathing, stomach pain, nausea and vomiting, confusion, tiredness, loss of appetite, and excessive thirst.

Severe cases of DKA can lead to coma. Diabetic ketoacidosis can happen to anyone with diabetes but it is not common in people with type 2 diabetes.

In 2016, Health Canada reviewed the potential risk of DKA in patients using SGLT2 inhibitors and concluded that this class of drugs may increase the risk of DKA. At that time, the CPM for all products in the drug class were updated to include this risk, as well as the symptoms associated with DKA and recommendations on what to do if patients experienced these symptoms. Diabetic ketoacidosis generally resolves within 48 hours with standard management, including discontinuing the medication.

In 2023, following a manufacturer requested labelling update for canagliflozin-containing products [Invokana (canagliflozin) and Invokamet (canagliflozin / metformin)] to include the risk of prolonged DKA despite stopping treatment as part of standard DKA management, Health Canada reviewed this potential risk to determine the need for labelling changes across the SGLT2 inhibitor drug class. Health Canada also reviewed the potential risk of incident DKA after temporary treatment cessation prior to surgical procedures for SGLT2 inhibitors to determine the optimal time to stop these medications before scheduled surgery.

In this review, DKA was considered prolonged if it started during treatment with SGLT2 inhibitors and lasted 3 or more days after treatment was stopped as part of standard management. Incident DKA occurred after treatment with SGLT2 inhibitors was stopped before a planned surgery, and while the patient was recovering from the surgery. Patients often need to fast before surgery or other invasive procedures, which may also increase the risk of DKA in patients with type 2 diabetes.

Use in Canada

- Sodium-glucose cotransporter-2 inhibitors are a class of prescription drugs authorized for sale in Canada, to be used with diet and exercise, to lower blood sugar levels in adults with type 2 diabetes. Some SGLT2 inhibitors are also authorized to treat heart failure or chronic kidney disease in patients with or without diabetes.

- Sodium-glucose cotransporter-2 inhibitors have been marketed in Canada since 2014 and are used alone [Invokana, Forxiga (dapagliflozin), and Jardiance (empagliflozin)] or in combination with metformin [Invokamet, Xigduo (dapagliflozin / metformin) and Synjardy (empagliflozin / metformin)]. Various generic SGLT2 inhibitor products are also available in Canada. All SGLT2 inhibitors are currently available as oral tablets.

- Over the past 5 years, more than 30 million prescriptions for SGLT2 inhibitors have been dispensed by Canadian retail pharmacies. Overall, there has been a steady increase in prescriptions for all SGLT2 inhibitors during this time. Empagliflozin is the most commonly prescribed SGLT2 inhibitor in Canada.

Safety Review Findings

- Health Canada reviewed information from searches of the Canada Vigilance database[a] and the scientific literature.

- **Prolonged DKA after stopping SGLT2 inhibitor treatment as part of standard DKA management**

    - Health Canada reviewed 167 cases (144 Canadian and 23 international) of DKA in adult patients with type 2 diabetes taking SGLT2 inhibitors where treatment was stopped when DKA was suspected or confirmed (67 in patients taking empagliflozin, 31 in patients taking dapagliflozin and 69 in patients taking canagliflozin). Twenty-six of the 167 cases (3 Canadian) were from the published literature.
    - Diabetic ketoacidosis was prolonged in over half of the Canadian cases despite stopping SGLT2 inhibitor treatment.
    - Diabetic ketoacidosis lasted 18 days in 1 Canadian patient taking dapagliflozin. There were 6 Canadian cases of DKA lasting longer than 10 days in patients taking canagliflozin, which included 1 case where DKA lasted 21 days. There were no cases of DKA lasting longer than 10 days in patients taking empagliflozin.
    - Health Canada's review could not confirm a definitive link between the use of SGLT2 inhibitors and prolonged DKA despite stopping treatment because other factors, such as pre-existing liver or kidney disease, restricted food intake, stress of surgery, dehydration and other medications, may have been involved in the prolongation of DKA. However, a possible link could not be ruled out.

- **Incident DKA after stopping treatment before scheduled surgery**

    - Health Canada reviewed 44 cases (10 Canadian and 34 international) from the published literature of DKA following surgery in adult patients with type 2 diabetes taking SGLT2 inhibitors where treatment was temporarily stopped before surgery (22 in patients taking empagliflozin, 7 in patients taking dapagliflozin, and 15 in patients taking canagliflozin). Forty-one of the 44 cases reviewed were in patients who stopped treatment with SGLT2 inhibitors 2 days or less before surgery (20 of the 22 patients taking empagliflozin, 6 of the 7 patients taking dapagliflozin, and all patients taking canagliflozin).
    - No relationship was found between the number of days before surgery the treatment with SGLT2 inhibitor was stopped and the onset of DKA.
    - Health Canada also reviewed 5 epidemiologic studies, which indicated that temporarily stopping treatment with SGLT2 inhibitors for a longer period of time before surgery may lower the risk of incident DKA after surgery by 30-50%. However, none of these studies investigated the optimal time for temporary treatment cessation of SGLT2 inhibitors before surgery and there were study limitations.

[a] Canadian reports can be accessed through the Canada Vigilance Online Database.

- Based on the pharmacology of SGLT2 inhibitors, stopping treatment at least 3 days before surgery or other invasive procedure requiring prolonged fasting is reasonable to ensure that the drug has enough time to be eliminated from the body.

Conclusions and Actions

- While a definitive link could not be confirmed, Health Canada's review of the available information could not rule out a possible drug class effect for the risk of prolonged DKA despite stopping SGLT2 inhibitor treatment as part of standard management in adult patients with type 2 diabetes.
- Health Canada's review of the available information also identified a number of cases of incident DKA following surgery in adult patients with type 2 diabetes taking SGLT2 inhibitors where treatment was temporarily stopped 2 days or less before surgery.
- To reduce the potential risk of incident DKA, Health Canada recommends stopping treatment with SGLT2 inhibitors at least 3 days before surgery or other invasive procedures requiring prolonged fasting, which is consistent with recommendations from Canadian and international diabetes associations and the U.S. Food and Drug Administration. Health Canada also recommends monitoring for DKA following the surgery or procedure, with the decision to reinitiate treatment with SGLT2 inhibitors to be made by the healthcare professional.
- Health Canada is working with the manufacturers to update and align the CPM for SGLT2 inhibitors to include a warning about the risk of prolonged DKA despite stopping treatment as part of standard DKA management in adult patients with type 2 diabetes, and a recommendation for temporary treatment cessation before a surgical procedure.
- Health Canada will also inform healthcare professionals about these updates through a Health Product InfoWatch communication.
- Health Canada encourages consumers and healthcare professionals to report any side effects related to the use of SGLT2 inhibitors, and other health products, to the Canada Vigilance Program.
- Health Canada will continue to monitor safety information involving SGLT2 inhibitors, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

Additional Information

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international information and what is known about the use of SGLT2 inhibitors both in Canada and internationally.

For additional information, contact the Marketed Health Products Directorate.