

### FDA Drug Safety Communication

FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)

#### Safety Announcement

**[6-14-2016]** The U.S. Food and Drug Administration (FDA) has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

**Patients** should seek medical attention immediately if they experience signs and symptoms of acute kidney injury. This is a serious condition in which the kidneys suddenly stop working, causing dangerous levels of wastes to build up in the body. Signs and symptoms of acute kidney injury may include decreased urine or swelling in the legs or feet. Patients should not stop taking their medicine without first talking to their health care professionals. Doing so can lead to uncontrolled blood sugar levels that can be harmful.

**Health care professionals** should consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other medications such as diuretics, blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.

Canagliflozin and dapagliflozin are prescription medicines used with diet and exercise to help lower blood sugar in adults with type 2 diabetes. They belong to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin and dapagliflozin lower blood sugar by causing the kidneys to remove sugar from the body through the urine. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

From March 2013, when canagliflozin was approved, to October 2015, FDA received reports of 101 confirmable cases\* of acute kidney injury, some requiring hospitalization and dialysis, with canagliflozin or dapagliflozin use (see Data Summary). This number includes only reports submitted to FDA, so there are likely additional cases about which we are unaware. In approximately half of the cases, the events of acute kidney injury occurred within 1 month of starting the drug, and most patients improved after stopping it. Some cases occurred in patients

who were younger than 65 years. Some patients were dehydrated, had low blood pressure, or were taking other medicines that can affect the kidneys.

We urge health care professionals and patients to report side effects involving canagliflozin, dapagliflozin, or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

<sup>1</sup>The cases were reported to the [FDA Adverse Event Reporting System \(FAERS\)](#).

### **Facts about canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)**

- Canagliflozin and dapagliflozin are prescription medicines that are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. They belong to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors.
- Canagliflozin and dapagliflozin are available as single-ingredient products under the brand names Invokana and Farxiga. They are also available in combination with the diabetes medicine metformin under the brand names Invokamet and Xigduo XR.
- Canagliflozin and dapagliflozin lower blood sugar by causing the kidneys to remove sugar from the body through the urine.
- In addition to acute kidney injury, some other possible side effects of canagliflozin or dapagliflozin include low blood pressure, a condition of too much acid in the blood called ketoacidosis, serious urinary tract infections, and yeast infections.
- Combining canagliflozin or dapagliflozin with other prescription diabetes medicines can increase the likelihood of low blood sugar.
- During the 12 month period from October 2014 through September 2015, approximately 1.5 million unique patients received a dispensed prescription for canagliflozin or dapagliflozin-containing product through outpatient U.S. retail pharmacies.<sup>1</sup>

### **Additional Information for Patients**

- Cases of acute kidney injury, some requiring hospitalization and dialysis, have been reported in patients receiving canagliflozin (Invokana, Invokamet) or dapagliflozin (Farxiga, Xigduo XR).
- About half of the cases occurred within 1 month of starting canagliflozin or dapagliflozin, and most patients improved after stopping the drug.
- Before starting canagliflozin or dapagliflozin, tell your health care professional if you are taking other medicines that may also affect the kidneys such as water pills, blood pressure medicines, or nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, or naproxen.
- Seek medical attention immediately if you experience signs and symptoms while taking these medicines such as:
  - Decreased urine
  - Swelling in your legs or feet
- Talk with your health care professional immediately if you are:
  - Eating or drinking less due to illness or fasting
  - Losing fluids due to vomiting, diarrhea, or excessive heat exposure

Your health care professional may determine it is appropriate to temporarily stop taking canagliflozin or dapagliflozin in these situations.

- Do not stop or change your diabetes medicines without first talking to your health care professional. Doing so can lead to uncontrolled blood sugar levels that can be harmful. Over time, uncontrolled blood sugar levels can cause serious problems, including blindness, nerve and kidney damage, and heart disease.
- Read the patient [Medication Guide](#) you receive with your canagliflozin or dapagliflozin prescriptions. It explains the benefits and risks associated with the medicine.
- Talk to your health care professional if you have questions or concerns about canagliflozin, dapagliflozin, or any other diabetes medicines.
- Report side effects from canagliflozin, dapagliflozin, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Additional Information for Health Care Professionals**

- Postmarketing cases of acute kidney injury, some requiring hospitalization and dialysis, have been reported in patients receiving canagliflozin (Invokana, Invokamet) or dapagliflozin (Farxiga, Xigduo XR).
- In approximately half of the cases, acute kidney injury occurred within 1 month of starting the drug, and most patients improved after discontinuing the drug.
- Before initiating canagliflozin or dapagliflozin, consider factors that may predispose patients to acute kidney injury. These include hypovolemia, chronic renal insufficiency, congestive heart failure, and concomitant medications such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs).
- Evaluate renal function prior to initiating canagliflozin or dapagliflozin and monitor periodically thereafter.
- Consider temporarily discontinuing canagliflozin or dapagliflozin in any setting of reduced oral intake such as acute illness or fasting, or with fluid losses such as gastrointestinal illness or excessive heat exposure.
- Monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue canagliflozin or dapagliflozin promptly and institute treatment.
- Encourage patients to read the [Medication Guide](#) they receive with their canagliflozin or dapagliflozin prescriptions.
- Report adverse events involving canagliflozin, dapagliflozin, or other drugs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Data Summary**

A search of the [FDA Adverse Event Reporting System \(FAERS\) database](#) from March 29, 2013, to October 19, 2015, identified 101 cases of acute kidney injury with sufficient detail to confirm the diagnosis and demonstrate a temporal relationship with canagliflozin (73 patients) and dapagliflozin (28 patients). Hospitalization for evaluation and management of acute kidney injury was necessary in 96 of the 101 cases, and 22 cases involved admission to an intensive care

unit. Four deaths occurred during hospitalization, 2 of which were cardiac-related. Fifteen patients received dialysis, and of these, 3 patients had a history of chronic kidney disease or previous acute kidney injury, and 6 reported concomitant use of both an angiotensin-converting enzyme (ACE) inhibitor and a diuretic. In 58 cases, the time to onset of acute kidney injury occurred within one month or less of initiating the drug.

The median age of the patients was 57 years (range 28-79 years). Among the 84 cases that reported an age, more than half were in patients who were 60 years or younger. Of the 101 cases, 51 reported concomitant ACE inhibitor use, 26 reported concomitant diuretic use, and 6 reported concomitant nonsteroidal anti-inflammatory drug (NSAID) use. A prior history of chronic kidney disease was reported in 10 of the 101 cases. In some cases, dehydration or hypotension was reported. Forty-five of the 101 cases reported a change in renal function (serum creatinine (SCr) or estimated glomerular filtration rate (eGFR)) at the time of diagnosis. The median elevation of SCr from baseline in 32 patients was 1.6 mg/dL. In 13 cases that only reported eGFR at baseline and during the acute kidney injury event, the median decrease in eGFR was 46 mL/min/1.73 m<sup>2</sup>.

In the 78 cases reporting drug discontinuation, 56 cases reported improvement, demonstrating reversibility of this adverse event in a majority of cases. Eleven patients did not recover, which included the 4 deaths noted previously. Three patients recovered with sequelae upon discontinuation, suggesting that kidney injury may not be fully reversible in some situations.

## Reference

1. IMS Health, Total Patient Tracker (TPT), DATA 2015-2308 SGLT2 Inhibitor DSC.xlsx.

## Related Information

- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)