U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

# FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)

This information is an update to the FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate issued on May 18, 2016.

**Safety Announcement**

**[5-16-2017]** Based on new data from two large clinical trials, the U.S. Food and Drug Administration (FDA) has concluded that the type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations. We are requiring new warnings, including our most prominent *Boxed Warning*, to be added to the canagliflozin drug labels to describe this risk.

**Patients** taking canagliflozin should notify your health care professionals right away if you develop new pain or tenderness, sores or ulcers, or infections in your legs or feet. Talk to your health care professional if you have questions or concerns. Do not stop taking your diabetes medicine without first talking to your health care professional.

**Health care professionals** should, before starting canagliflozin, consider factors that may predispose patients to the need for amputations. These factors include a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Monitor patients receiving canagliflozin for the signs and symptoms described above and discontinue canagliflozin if these complications occur.

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

Final results from two clinical trials – the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus) – showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment. The CANVAS

trial showed that over a year's time, the risk of amputation for patients in the trial were equivalent to:

- 5.9 out of every 1,000 patients treated with canagliflozin
- 2.8 out of every 1,000 patients treated with placebo

The CANVAS-R trial showed that over a year's time, the risk of amputation for patients in the trial were equivalent to:

- 7.5 out of every 1,000 patients treated with canagliflozin
- 4.2 out of every 1,000 patients treated with placebo

Amputations of the toe and middle of the foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Some patients had more than one amputation, some involving both limbs.

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

**Facts about canagliflozin (Invokana, Invokamet, Invokamet XR)**

- Canagliflozin is a prescription medicine that is used with diet and exercise to lower blood sugar in adults with type 2 diabetes. It belongs to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors.
- Canagliflozin is available as a single-ingredient product under the brand name Invokana, and also in combination with the diabetes medicine metformin under the brand names Invokamet and Invokamet XR.
- Canagliflozin lowers blood sugar by causing the kidneys to remove sugar from the body through the urine.
- Other side effects of canagliflozin include low blood pressure, a condition of too much acid in the blood called ketoacidosis; kidney problems; a high amount of potassium in the blood; serious urinary tract infections; low blood sugar when combined with other prescription diabetes medicines; yeast infections; bone breaks; and increased cholesterol.

**Additional Information for Patients**

- The type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) can increase your risk of leg and foot amputations. This risk may be higher for some people, including those who have peripheral vascular disease, neuropathy (nerve damage), or diabetic foot ulcers (sores), or who have a history of prior amputation.
- Contact your health care professional right away if you develop new pain or tenderness, sores or ulcers, or infections in your legs or feet.
- Your health care professional may determine it is appropriate for you to stop taking canagliflozin 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 every time you receive a canagliflozin prescription because the information might change. The Medication Guide explains the benefits and risks associated with the medicine.
- Talk to your health care professional if you have questions or concerns about canagliflozin or any other diabetes medicines.
- Report side effects from canagliflozin 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**

- The type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of lower limb amputations.
- Before initiating canagliflozin, consider factors in the patient's history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.
- Monitor patients receiving canagliflozin for signs and symptoms of infection, new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue canagliflozin if these complications occur.
- Inform patients that canagliflozin is associated with an increased risk of amputations. Instruct patients to monitor for the signs and symptoms described above and to seek medical advice immediately if they develop.
- In the clinical trials, amputations of the toe and mid-foot occurred most frequently; however, amputations involving the leg, below and above the knee, also occurred.
- Lower limb infections, gangrene, diabetic foot ulcers, and ischemia were the most common precipitating medical events leading to the need for an amputation.
- Encourage patients to read the Medication Guide they receive with their canagliflozin prescriptions.
- Report adverse events involving canagliflozin or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

**Data Summary**

An approximately two-fold increased risk of lower limb amputations associated with canagliflozin use was observed in two large, randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. These trials were CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus). Patients in the CANVAS and CANVAS-R trials were followed for an average of 5.7 and 2.1 years, respectively.

In CANVAS, the risk of lower limb amputations was 5.9 amputations per 1,000 patients per year for canagliflozin compared to 2.8 amputations per 1,000 patients per year for

placebo (Number Needed to Harm: 323). In CANVAS-R, the risk of lower limb amputations was 7.5 amputations per 1,000 patients per year for canagliflozin compared to 4.2 amputations per 1,000 patients per year for placebo (Number Needed to Harm: 270). The risk of lower limb amputations was observed at both the 100 mg and 300 mg doses. The amputation results for CANVAS and CANVAS-R are shown in Tables 1 and 2 below.

Overall, amputations of the toe and mid-foot were the most frequent (99 out of 140 patients with amputations receiving canagliflozin in the two trials); however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving canagliflozin in the two trials). Some patients had more than one amputation, some involving both limbs. Lower limb infections, gangrene, diabetic foot ulcers, and ischemia were the most common precipitating medical events leading to an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Table 1. CANVAS Amputations

| | **Placebo N=1,441** | **Canagliflozin 100 mg N=1,445** | **Canagliflozin 300 mg N=1,441** | **Canagliflozin (pooled) N=2,886** |
|---|---|---|---|---|
| Patients with an amputation, n (%) | 22 (1.5) | 50 (3.5) | 45 (3.1) | 95 (3.3) |
| Total amputations* | 33 | 83 | 79 | 162 |
| Amputation incidence rate (per 1,000 patient-years) | 2.8 | 6.2 | 5.5 | 5.9 |
| Hazard ratio (95% CI) | — | 2.24 (1.36, 3.69) | 2.01 (1.20, 3.34) | 2.12 (1.34, 3.38) |

* Some patients had more than one amputation.

Table 2. CANVAS-R Amputations

| | **Placebo N=2,903** | **Canagliflozin 100 mg (with up-titration to 300 mg) N=2,904** |
|---|---|---|
| Patients with an amputation, n (%) | 25 (0.9) | 45 (1.5) |
| Total amputations* | 36 | 59 |
| Amputation incidence rate (per 1,000 patient-years) | 4.2 | 7.5 |
| Hazard ratio (95% CI) | — | 1.80 (1.10, 2.93) |

* Some patients had more than one amputation.

**Related Information**

Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors

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