Canagliflozin – New boxed warning

- On May 16, 2017, the FDA announced that a new *Boxed Warning* regarding an increased risk of leg and foot amputations will be added to all canagliflozin [Invokana®, Invokamet® (canagliflozin/metformin), Invokamet® XR (canagliflozin/metformin extended-release)] drug labels.
    - Similar updates will made to other safety sections of the canagliflozin drug labels.
- Canagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor used as an adjunct with diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).
- Healthcare providers 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.
- Patients receiving canagliflozin therapy should be monitored for signs and symptoms of infection, new pain or tenderness, sores, or ulcers involving lower limbs, and discontinue canagliflozin if these complications occur.
- Patients should discuss any questions they may have regarding canagliflozin or any other diabetes medicines with their healthcare provider and not stop taking their medicine without discussing with their healthcare provider.
    - Immediately stopping or changing diabetes therapy may lead to uncontrolled blood sugar levels that can be harmful. Over time, uncontrolled blood sugar levels can cause blindness, nerve and kidney damage, and heart disease.
- The safety update was based on data from the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with T2DM) studies which showed an approximately two-fold increased risk of lower limb amputations associated with canagliflozin use in patients with T2DM who had either established CV disease or were at risk for CV disease. Refer to the tables below for amputation data.
    - 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 and some involved both limbs.
    - Lower limb infections, gangrene, diabetic foot ulcers, and ischemia were the most common precipitating medical events leading to the need for an amputation.

CANVAS

	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 ≥ 1 amputation*

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CANVAS-R

	Placebo (n = 2,903)	Canagliflozin 100 mg (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 ≥ 1 amputation*

- This safety communication is an update to an FDA announcement released in 2016.