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IN BRIEF

## Canagliflozin and Lower Limb Amputations

The FDA has removed a boxed warning from the labeling of products containing the sodium-glucose co-transporter 2 (SGLT2) inhibitor canagliflozin *(Invokana, Invokamet, Invokamet XR)* that described an increased risk of lower limb amputation associated with use of the drug.[1] Package inserts for canagliflozin products still contain a standard warning about a risk of lower limb amputation.

Canagliflozin was approved by the FDA in 2013 to improve glycemic control in patients with type 2 diabetes.[2] The boxed warning for amputation risk was added to its label in 2017 based on the results of two randomized, double-blind trials (CANVAS, CANVAS-R) in a total of 10,142 patients with type 2 diabetes and high cardiovascular (CV) risk. The incidence of toe, foot, or leg amputation was higher with addition of canagliflozin to standard treatment than with addition of placebo (6.3 vs 3.4 cases per 1000 patient-years).[3] Because these trials also demonstrated that use of canagliflozin had CV benefits, the drug was approved to reduce the risk of major adverse CV events in adults with type 2 diabetes and established CV disease in 2018.[4]

In 2019, based on the results of a randomized, double-blind trial (CREDENCE) in 4401 patients, canagliflozin was approved by the FDA to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with type 2 diabetes and diabetic nephropathy with macroalbuminuria. The incidence of lower limb amputation in CREDENCE was not significantly greater with addition of canagliflozin to standard treatment than with addition of placebo (12.3 vs 11.2 cases per 1000 patient-years).[4,5]

Based on these recent efficacy and safety data, the FDA concluded that the risk-to-benefit profile of canagliflozin no longer warranted the inclusion of a boxed warning in the drug's label.[1] Patients taking canagliflozin should still be monitored for new pain, tenderness, sores, ulcers, and infections in the legs and feet.

The SGLT2 inhibitors dapagliflozin *(Farxiga)* and empagliflozin *(Jardiance)* have not been associated with an increased risk of lower limb amputation.[4] Ertugliflozin *(Steglatro)*, a fourth SGLT2 inhibitor, has been associated with an increased risk of low-traumatic lower limb amputation in clinical trials (0.2% with 5 mg and 0.5% with 15 mg vs 0.1% with a comparator regimen)[6]; the drug's label contains a warning similar to that in the revised canagliflozin labeling. ■

1. FDA drug safety communication: FDA removes boxed warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). August 26, 2020. Available at: www.fda.gov/media/141533/download. Accessed September 10, 2020.
2. Canagliflozin (Invokana) for type 2 diabetes. Med Lett Drugs Ther 2013; 55:37.
3. B Neal et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377:644.
4. Drugs for type 2 diabetes. Med Lett Drugs Ther 2019; 61:169.
5. V Perkovic et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019; 380:2295.
6. Ertugliflozin for type 2 diabetes. Med Lett Drugs Ther 2018; 60:70.



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