

**Important Safety Information on INVOKANA® (canagliflozin) and
INVOKAMET® (canagliflozin and metformin) -
Risk of Lower Limb Amputation**



2017/09/06

Audience

Healthcare professionals including internal medicine specialists, endocrinologists, cardiologists, nephrologists, general or family practitioners, emergency healthcare professionals, critical care physicians, diabetic and homecare nurses, certified diabetes educators and pharmacists.

Key messages

- **An approximately two-fold increased risk of surgical lower limb amputation (primarily of the toe and midfoot but also of the leg) has been observed in two long-term clinical studies in type 2 diabetes patients with established cardiovascular disease (CVD) or at least two risk factors for CVD treated with INVOKANA.**
- **Healthcare professionals are advised to:**
 - **consider factors in the patient history that may increase the risk for lower limb amputation before initiating INVOKANA or INVOKAMET.**
 - **carefully monitor patients with a higher risk for amputation.**
 - **counsel patients about the importance of routine preventative foot care and adequate hydration.**
 - **discontinue INVOKANA or INVOKAMET treatment in patients who develop a significant complication which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.**
- **The Canadian Product Monographs of INVOKANA and INVOKAMET will be updated to reflect this safety information.**

What is the issue?

An increase in the incidence rate of lower limb amputation-primarily of the toe and midfoot, but also of the leg-has been seen in the integrated CANagliflozin cardioVascular Assessment Study (CANVAS) Program (0.63 per 100 patient-years in patients treated with canagliflozin versus 0.34 per 100 patient-years in patients

treated with placebo). The CANVAS Program was comprised of CANVAS and CANVAS-R, two large, long-term, randomized, placebo-controlled trials evaluating long-term cardiovascular outcomes in 10,142 individuals with type 2 diabetes with established cardiovascular disease (CVD) or at least two risk factors for CVD who were treated with canagliflozin.¹

Products affected

Brand Name	Medicinal Ingredients	Manufacturer
INVOKANA®	canagliflozin	Janssen Inc.
INVOKAMET®	canagliflozin and metformin	Janssen Inc.

Background information

Canagliflozin is a member of a class of drugs called sodium glucose co-transporter type 2 (SGLT2) inhibitors indicated as oral antihyperglycemic agents for the treatment of patients with type 2 diabetes.

The increase in the incidence rate of lower limb amputation (mostly affecting the toe and midfoot, but also of the leg) occurred as early as the first 26 weeks of therapy during long-term clinical studies, CANVAS and CANVAS-R, in patients taking INVOKANA. Patients in the CANVAS and CANVAS-R studies were followed for an average of 5.7 and 2.1 years, respectively.

This increased risk was independent of predisposing risk factors, although the absolute risk was higher in patients with previous amputations, existing peripheral vascular disease or neuropathy. No dose response was observed.

Lower limb infections, diabetic foot ulcers, peripheral arterial disease, and gangrene were the most common medical events associated with the need for an amputation in both treatment groups.

A higher incidence of amputation was not observed across 12 other completed Phase 3 or 4 clinical trials which included a general diabetic population of 8,114 patients (the majority of which were without established CVD) with a mean exposure of 0.9 years.

Information for consumers

Canagliflozin is a type of medication used to treat type 2 diabetes. It works by preventing the kidneys from reabsorbing sugar into the blood. Instead, the sugar is excreted in the urine. An increase in surgical amputations of the toe and middle of the foot, was seen in a long-term clinical study, especially in patients at high risk of heart disease.

Patients taking INVOKANA or INVOKAMET should be advised to talk to their healthcare professional right away if they have new pain or tenderness or any sores, ulcers, or infections involving the leg or foot. Patients and healthcare professionals should also watch out for signs of poor circulation, such as bluish, cold skin and poor hair and toe nail growth. Proper foot care and adequate hydration are recommended.

Consumers should contact their healthcare professional for more information.

Information for healthcare professionals

Healthcare providers are reminded to follow established diabetes care practice guidelines in patients treated with canagliflozin:

- Consider factors in the patient history that may increase the risk for amputation.
- Carefully monitor patients with risk factors for amputation events, e.g., patients with previous amputations, existing peripheral vascular disease or neuropathy.
- Counsel patients about the importance of routine preventive foot care, good hydration, and the signs and symptoms of volume depletion.
- Monitor patients for signs and symptoms of volume depletion and ensure that hydration is sufficient to prevent volume depletion in line with recommendations in the product information. Use of diuretics may further exacerbate dehydration.
- Advise patients to notify their healthcare provider if they develop sores, ulceration, discoloration, infection, new lower extremity pain or tenderness.
- Initiate early treatment for foot problems for, but not limited to, ulceration, infection, new pain or tenderness.
- Discontinue canagliflozin treatment in patients who develop a significant complication, such as a lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

Action taken by Health Canada

In October 2016, the Product Monographs for INVOKANA and INVOKAMET were updated to include adverse reaction and consumer information discussing the risk of lower limb amputation based on interim results of the CANVAS study. Health Canada is currently working with the manufacturer to update the Canadian Product Monographs regarding this safety information to reflect the final results of the CANVAS clinical trials. Health Canada is also communicating this important safety information to Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system.

Report health or safety concerns

Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any adverse event or other serious or unexpected side effects to INVOKANA and INVOKAMET should be reported to the manufacturer, Janssen Inc., or to Health Canada.

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To correct your mailing address or fax number, contact Janssen Inc.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on [Adverse Reaction Reporting](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate
E-mail: mhpd_dpssc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,

Original signed by



Dr. Cathy Lau
Vice President, Regulatory Affairs and Quality Management
Janssen Inc.

References

¹ Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. [Epub ahead of print]. NEJM. 2017. Published June 12. doi: 10.1056/NEJMoa1611925.

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