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

Drug Safety Communications

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

Safety Announcement

[5-18-2016] The U.S. Food and Drug Administration (FDA) is alerting the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with the diabetes medicine canagliflozin (Invokana, Invokamet). We have not determined whether canagliflozin increases the risk of leg and foot amputations. We are currently investigating this new safety issue and will update the public when we have more information.

Patients should not stop or change their diabetes medicines without first talking to their health care professional. Doing so can lead to uncontrolled blood sugar levels that can be harmful. Over time, this can cause serious problems, including blindness, nerve and kidney damage, and heart disease. Patients taking canaglifozin should notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

Health care professionals should follow the recommendations in the canagliflozin drug labels. Monitor patients for the signs and symptoms described above and advise patients to seek medical advice if they experience them.

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. It is available as a single-ingredient product under the brand name Invokana and also in combination with the diabetes medicine metformin under the brand name Invokamet.

In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial, the trial's independent data monitoring committee (IDMC) identified an increased risk of leg and foot amputations. The amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment. An interim analysis showed that over a year's time, the risks of amputation for patients in the trial were equivalent to:

- 7 out of every 1,000 patients treated with 100 mg daily of canagliflozin
- 5 out of every 1,000 patients treated with 300 mg daily of canagliflozin

- 3 out of every 1,000 patients treated with placebo

Patients in the CANVAS trial have been followed for an average of 4.5 years to date. The IDMC has recommended, based on an overall assessment, that the CANVAS trial continue.

The IDMC has also reported that a second, similar trial evaluating canagliflozin, the CANVAS-R trial, has not shown the same risks of increased leg and foot amputations to date. Patients in the CANVAS-R trial have been followed for an average of 9 months.

We are continuing to evaluate this safety issue and will update the public when we have more information. We urge health care professionals and patients to report side effects involving canagliflozin or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Related Information

- Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
- Think It Through: Managing the Benefits and Risks of Medicines