

FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density

Safety Announcement

[9-10-2015] The U.S. Food and Drug Administration (FDA) has strengthened the warning for the type 2 diabetes medicine canagliflozin (Invokana, Invokamet) related to the increased risk of bone fractures and added new information about decreased bone mineral density. Bone mineral density relates to the strength of a person's bones. To address these safety concerns, we added a new *Warning and Precaution* and revised the *Adverse Reactions* section of the Invokana and Invokamet drug labels.

Health care professionals should consider factors that contribute to fracture risk prior to starting patients on canagliflozin. Patients should talk to their health care professionals about factors that may increase their risk for bone fracture. Patients should not stop or change their diabetes medicines without first talking to their health care professional.

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. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. 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.

Information about the risk of bone fractures was already in the *Adverse Reactions* section of the drug label at the time of canagliflozin's approval. Based on updated information about bone fractures from several clinical trials, we revised the drug label and added a new *Warning and Precaution*. The additional data confirm the finding that fractures occur more frequently with canagliflozin than placebo, which is an inactive treatment. Fractures can occur as early as 12 weeks after starting the drug. In the clinical trials, when trauma occurred prior to a fracture, it was usually minor, such as falling from no more than standing height.

In addition, we have added new information about the risk of decreased bone mineral density to the canagliflozin label. A clinical trial that we required the manufacturer of canagliflozin to conduct evaluated changes to bone mineral density over two years in 714

elderly individuals and showed that canagliflozin caused greater loss of bone mineral density at the hip and lower spine than a placebo. This new safety information has been added to the *Adverse Reactions* section of the drug label.

We are continuing to evaluate the risk of bone fractures with other drugs in the SGLT2 inhibitor class, including dapagliflozin (Farxiga, Xigduo XR) and empagliflozin (Jardiance, Glyxambi, Synjardy), to determine if additional label changes or studies are needed. We urge health care professionals and patients to report side effects involving canagliflozin or other SGLT2 inhibitors to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Facts about canagliflozin (Invokana, Invokamet)

- Canagliflozin is a prescription medicine that is used along 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 name Invokamet.
- Canagliflozin lowers blood sugar by causing the kidneys to remove sugar from the body through the urine.
- In addition to bone fractures and decreased bone mineral density, some other possible side effects of canagliflozin include dehydration, kidney problems, low blood sugar when it is combined with other prescription diabetes medicines, a high amount of potassium in the blood, increased cholesterol, and yeast infections.
- Approximately 1.1 million unique patients received canagliflozin prescriptions, and approximately 41,000 unique patients received combination canagliflozin-metformin prescriptions from U.S. outpatient retail pharmacies during the 12-month period from July 2014 through June 2015.¹

Additional Information for Patients

- Bone fractures have been seen in patients taking the type 2 diabetes medicine canagliflozin, sold under the brand names Invokana and Invokamet. Fractures can occur as early as 12 weeks after starting canagliflozin.
- Canagliflozin has also been linked to decreases in bone mineral density at the hip and lower spine. Bone mineral density relates to the strength of a person’s bones.
- Talk to your health care professional about factors that may increase your risk of bone fracture.
- Do not stop or change your diabetes medicines without first talking to your health care professional. When untreated, diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.
- Read the patient Medication Guide you receive with your canagliflozin prescriptions. It explains the benefits and risks associated with the use of the medicine. You may access Medication Guides by clicking on the following links: [Invokana](#) and [Invokamet](#).

- Talk to your health care professional if you have questions or concerns about canagliflozin or any of your other diabetes medicines.
- Report side effects from canagliflozin 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

- An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using canagliflozin.
- Canagliflozin has also been linked to decreases in bone mineral density at the hip and lumbar spine.
- Consider factors that contribute to fracture risk prior to initiating canagliflozin.
- Counsel patients about factors that may contribute to bone fracture risk.
- Encourage patients to read the Medication Guide they receive with their canagliflozin prescriptions.
- Report adverse events involving canagliflozin to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

The occurrence of bone fractures was evaluated in nine pooled clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator (includes placebo and active comparators), canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation, and were more likely to be low trauma (e.g., arising after falls from no more than standing height) and affect the upper extremities.

A double-blind, placebo-controlled clinical trial was conducted as part of an FDA-issued postmarketing requirement to evaluate the safety of canagliflozin in combination with current diabetes treatment. A total of 714 older patients (mean age 64 years, range 55 to 80 years) with type 2 diabetes inadequately controlled on current diabetes therapy (either diet and exercise alone or in combination with oral or parenteral agents) participated in the trial. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry. At 2 years, patients randomized to canagliflozin 100 mg and canagliflozin 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both canagliflozin doses and 0.4% at the distal forearm for patients randomized to canagliflozin 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to canagliflozin 100 mg was 0%.

References

1. IMS Health: Total Patient Tracker (TPT). July 2014 through June 2015. Extracted August 2015. File: DATA 2015- Canagliflozin DSC.