NATIONAL PBM BULLETIN

MAY 31, 2016

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

CANAGLIFLOZIN (INVOKANA®, INVOKAMET®) AND RISK OF AMPUTATIONS

I. ISSUE

The Food and Drug Administration (FDA) is currently investigating interim safety results from an ongoing clinical trial showing an increase in leg and foot amputations, mostly affecting the toes, in patients treated with canagliflozin (Invokana, Invokamet) for diabetes. FDA continues to evaluate this new safety issue and will update the public on whether canagliflozin increases the risk of leg and foot amputations as new data becomes available.

II. BACKGROUND

Canagliflozin (Invokana, Invokamet) is a sodium-glucose cotransporter-2 (SGLT2) inhibitor used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. It lowers blood sugar by decreasing reabsorption of filtered glucose in the kidney thereby increasing urinary glucose excretion.

III. DISCUSSION

The ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial identified an increased risk of leg and foot amputations that occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo.

- An interim analysis showed the risks of amputation for patients in the trial over approximately 1 year 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.

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.

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

FDA recommends that healthcare professionals:

- Monitor patients receiving canagliflozin (Invokana, Invokamet) for any new pain or tenderness, sores or ulcers, or infections in their legs or feet.
- Instruct patients taking canaglifozin to 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.
- Inform patients not to stop or change their diabetes medicines without first talking to their health care professional because doing so can lead to uncontrolled blood sugar levels that can cause harm.

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- Providers should continue to report any adverse reactions with the use of canagliflozin (Invokana, Invokamet) by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).

V. REFERENCES

FDA Drug Safety Communication: 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: http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm (Accessed May 18, 2016).

ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers and health care staff (e.g.,* ***primary care providers, endocrinology, including contract providers, etc****.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*