May 20, 2016

Subject: Interim Safety Analysis from an Ongoing Trial Observed a Higher Incidence of Lower Limb Amputations (Primarily of the Toe) in Patients Treated with INVOKANA® (canagliflozin). Reminder Regarding the Importance of Foot Care in Patients with Diabetes

Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information relating to the canagliflozin-containing medicines — INVOKANA® (canagliflozin) / INVOKAMET® (canagliflozin/metformin HCl) tablets for oral use.

- INVOKANA® is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- INVOKAMET® is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both canagliflozin and metformin is appropriate.
- INVOKANA® and INVOKAMET® are not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

New Safety Information and Background on the CANVAS Trial

The CANVAS trial is an ongoing, long-term, cardiovascular outcomes study of canagliflozin plus standard of care in individuals with type 2 diabetes who have either a prior history or high risk for cardiovascular events. The study includes 4330 randomized subjects with a mean follow-up time of approximately 4.5 years.
• In an interim safety analysis, the CANVAS Independent Data Monitoring Committee (IDMC) identified a two-fold higher incidence of lower limb amputation (primarily of the toe) in patients treated with canagliflozin. Amputation rates were 7 per 1000 patient-years with 100-mg daily canagliflozin, 5 per 1000 patient-years with 300-mg daily canagliflozin, and 3 per 1000 patient-years in the placebo group across all baseline risk factors for amputations. No dose response was seen with amputations.

• After consideration of all data in the CANVAS study, the IDMC recommended that the study should continue and actions should be taken to minimize the risk and inform the clinical trial participants of the risk; these are listed below in the prescriber actions.

• The IDMC has also reported that a second, similar ongoing trial, CANVAS-R, consisting of 5812 randomized patients followed for an average of 0.75 years, has not shown a statistically significant increase in lower limb amputations for canagliflozin to date. The IDMC is continuing to follow both CANVAS and CANVAS-R trials.

• No increased incidence of amputation with canagliflozin has been observed in post-marketing spontaneous reporting or across 12 other completed phase 3 and 4 clinical trials comprising more than 8100 individuals with a mean follow-up of 0.9 years (rate of amputation in canagliflozin-treated individuals was 0.6 per 1000 patient-years versus the rate in the placebo/comparator individuals of 2.3 per 1000 patient-years).

• This finding is being carefully investigated, and any mechanism behind the events is currently unknown. However, dehydration and volume depletion might play a role.

**Prescriber Actions:**

Healthcare providers are reminded of the following when treating patients with INVOKANA®/INVOKAMET®:

• To follow standard diabetes treatment guidelines, for example those of the American Diabetic Association, for routine preventive foot care (see Diabetes Care 2016, volume 39, supplement 1, page S72).

• Early recognition and treatment should be initiated for foot problems. These may include but are not limited to ulceration, infection, new pain or tenderness.

• Patients with risk factors for amputation events, such as previous amputations, existing peripheral vascular disease or neuropathy should be carefully monitored.

• As a precautionary measure, consider interruption of canagliflozin treatment when medical interventions are required for significant diabetic complications, such as lower extremity skin ulcer, osteomyelitis or gangrene, until the condition has resolved.

• Monitor patients for signs and symptoms of volume depletion or dehydration and take care that hydration is sufficient to prevent volume depletion, in line with recommendations in the package insert (USPI). Use of diuretics may further exacerbate dehydration.

Healthcare providers should also counsel patients about:

• The importance of routine preventive foot care.
• The importance of patients notifying their healthcare provider if they develop ulceration, discoloration, new pain or tenderness in their lower extremity.
• The importance to remain well hydrated and to educate them on the signs and symptoms of volume depletion.

Reporting Adverse Events

Healthcare professionals should report new cases of the adverse events described in this letter to 1-800-526-7736 or to FDA’s MedWatch Adverse Event Reporting program online (at www.fda.gov/MedWatch), by facsimile (1-800-FDA-0178), by telephone (1-800-FDA-1088), or by returning the postage-paid FDA form 3500 (which may be downloaded from www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf) by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.

Refer to the enclosed package insert for complete prescribing information or visit www.invokahanhcp.com/sites/www.invokahanhcp.com/files/prescribing-information-invokana.pdf for INVOKANA® or www.invokahanhcp.com/invokamet/prescribing-information.pdf for INVOKAMET®, including a BOXED WARNING.

For more information, please call the Janssen Medical Information Center at 1-800-526-7736.

Sincerely,

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