Direct Healthcare Professional Communication (Global): Advice on the Risk of Lower Limb Amputation (Primarily of the Toe) During Treatment with Canagliflozin-Containing Medicine: INVOKANA® (canagliflozin) and VOKANAMET (canagliflozin, metformin)

DATE: 16 August 2016

Dear Healthcare Professional:

Janssen-Cilag in agreement with Saudi Food and Drug Authority (SFDA) would like to inform you of the new important safety information relating to the canagliflozin-containing medicines: INVOKANA (canagliflozin) /VOKANAMET (canagliflozin/metformin).

Important New Safety Information for Use of INVOKANA®

- A two-fold higher incidence of lower limb amputation (primarily of the toe) has been seen in a clinical trial (CANVAS an on-going long-term cardiovascular outcomes trial of individuals with type 2 diabetes who are at high risk for cardiovascular events) treated with canagliflozin.

- The Independent Data Monitoring Committee (IDMC) for this study has noted a risk of 7 per 1000 patient-years in patients treated with 100mg canagliflozin and 5 per 1000 patient-years with patients treated with 300 mg versus 3 per 1000 patient-years in patients treated with placebo (mean follow-up ~4 years).

- This two-fold increased risk is 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.

- The issue is currently under investigation, and any mechanism behind the events is as yet unknown. However, dehydration and volume depletion might play a role in the development.

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

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- established diabetes guidelines emphasize routine preventive foot care;
- patients with risk factors for amputation events, e.g. patients with previous amputations, existing peripheral vascular disease or neuropathy should be carefully monitored;
- early treatment for foot problems should be initiated for, but not limited to, ulceration, infection, new pain or tenderness;
- as a precautionary measure, consideration should be given to stop canagliflozin treatment in patients who develop a significant complication, such as a lower-extremity skin ulcer, osteomyelitis or gangrene, at least until the condition has resolved;
- 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.

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 lower extremity pain or tenderness.
- Encouraging patients to remain well hydrated and educate them on the signs and symptoms of volume depletion.

Further information

- A higher incidence of amputation was not observed across 12 other completed Phase 3 or 4 clinical trials with a mean follow-up of 0.9 years (canagliflozin 0.6 per 1000 patient-years versus placebo/comparator 2 per 1000 patient-years) or in post-marketing spontaneous reporting.
- The IDMC has recommended, based on an overall assessment, that the CANVAS trial continue.

Reporting Adverse Events

Any suspected adverse events should be reported to the national spontaneous reporting system according to the national regulations.

SFDA (The National Pharmacovigilance and Drug Safety Center)
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Fax: +966-11-2057662
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Company contact points

If you have further questions or require additional information, please contact company scientific office at:
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Sincerely,

Khaled Soliman

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