29 April 2016

Direct Healthcare Professional Communication

Canagliflozin-Containing Medicines INVOKANA▼ (canagliflozin), VOKANAMET▼ (canagliflozin, metformin) and the risk of Lower Limb Amputation (Primarily of the Toe).

Dear Healthcare Professional,

Janssen-Cilag Limited in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) would like to inform you of the new important safety information relating to the canagliflozin-containing medicines: INVOKANA® (canagliflozin) /VOKANAMET® (canagliflozin/metformin).

Summary

- A two-fold higher incidence of lower limb amputation (primarily of the toe) has been seen in a clinical trial with canagliflozin (CANVAS an on-going long-term cardiovascular outcomes trial).
- The risk in the canagliflozin groups was 6 per 1000 patient years, compared with 3 per 1000 patient years with placebo.
- This increased risk was observed 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 that in patients treated with canagliflozin:

- standard diabetes treatment guidelines for routine preventive foot care are important;
- 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 including, but not limited to, ulceration, infection, new pain or tenderness;
- as a precautionary measure, consideration should be given to stop canagliflozin treatment in patients that develop a significant complication, such as a lower-extremity skin ulcer, osteomyelitis or gangrene, at least until the condition has resolved and under the presumption of increased alertness;
- monitor patients for signs and symptoms of loss of body water and salt and take care that hydration is sufficient to prevent volume depletion in line with recommendations of 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.

Background on the safety concern

The **CANVAS** trial (CANagliflozin cardioVascular Assessment Study) is an ongoing randomised, double-blind, placebo-controlled, 3-arm, parallel-group, multicentre study to evaluate the safety, tolerability, and cardiovascular (CV) risk with canagliflozin plus standard of care compared with placebo plus standard of care in subjects with type 2 diabetes mellitus who have either a prior history or high risk of CV disease. Subjects were randomly assigned to treatment with 1 of 2 doses of canagliflozin (100 mg or 300 mg) or matching placebo in a 1:1:1 ratio. The study is fully enrolled with 4,330 randomised subjects. The mean and median follow-up time is about 4.5 years.

Serious adverse event monitoring in this study has observed an approximately two-fold higher incidence of lower limb amputation (primarily of the toe) in the canagliflozin 100 mg (7/1000 patient-years) and 300 mg (5/1000 patient-years) treatment groups versus placebo (3/1000 patient-years) across all baseline risk factors for amputations
The CANVAS-R study, an ongoing outcome study with a similar population to CANVAS, showed a numerical imbalance with regard to amputation events (16 events in the canagliflozin group and 12 events in the placebo group). The estimated annualised incidence of amputations is 7 and 5 events per 1000 patient-year exposure in the canagliflozin and placebo group, respectively with no statistically significant difference.

A higher incidence of amputation was not observed across 12 other completed Phase 3/4 clinical trials with a mean follow-up of 0.9 years (0.6/1000 patient-years in canagliflozin and 2/1000 patient-years in control groups).

The issue is currently under investigation by the European Medicines Agency. Any new advice will be communicated promptly.

Call for reporting

▼These medicinal products are subject to additional monitoring to support risk management and it is therefore important to report any suspected adverse events.

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with these products in accordance with the national spontaneous reporting system.

Suspected adverse reactions should be reported to the Health Products Regulatory Authority, using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to the HPRA by calling (01) 676 4971.

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Suspected adverse reactions should also be reported to Janssen on tel: 0044 (0)1494 567 447, fax: 0044 (0)1494 567799 or by email at dsafety@its.jnj.com

Company contact points

If you have further questions or require additional information, please contact:
Janssen-Cilag Ltd Medical Information Department
Email: medinfo@janssen-cilag.co.uk
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Yours faithfully,

Medical Manager
Janssen Ireland