

Janssen-Cilag Pty Ltd
ABN 47 000 129 975

507 Mt Wellington Highway,
Mt Wellington, Auckland 1060
New Zealand
P.O. Box 62185, Sylvia Park Auckland 1644
Toll free tel: 0800 800 806
Fax: 649 588 1398



24 May 2016

INVOKANA[®] (canagliflozin): Advice on the Risk of Lower Limb Amputation Primarily of the Toe during treatment with canagliflozin

Dear Healthcare Professional

Janssen-Cilag Pty Ltd ('Janssen') would like to inform you of new important safety information relating to INVOKANA[®] (canagliflozin).

INVOKANA[®] is indicated for the treatment of adult patients with type 2 diabetes.¹

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 treated with canagliflozin (CANVAS an on-going long-term cardiovascular outcomes trial of individuals with type 2 diabetes who are at high risk for cardiovascular events).
- 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.
- The IDMC recommended that the CANVAS study should continue.
- 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.

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

- Established diabetes guidelines emphasise 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.

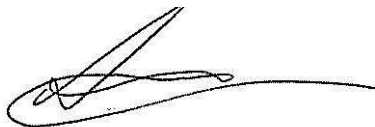
Reporting Adverse Events

Janssen is committed to monitoring the safety of our products. We encourage healthcare professionals to report any suspected adverse events for INVOKANA to the Centre for Adverse Reactions Monitoring (phone 03 479 7247 or email carmnz@otago.ac.nz) and/or Janssen Medical Information.

Please refer to the Data Sheet for complete prescribing information on INVOKANA[®], available from Medsafe (at <http://www.medsafe.govt.nz/>) or Janssen's Medical Information Department.

If you have further questions or require additional information, please contact Janssen Medical Information on 0800 800 806 or medinfo@janau.jnj.com

Sincerely



Dr Sophie Glover-Koudounas
Executive Director, Medical & Scientific Affairs ANZ
Janssen-Cilag Pty Ltd

References:

1. INVOKANA (canagliflozin) Data Sheet. 29 Feb 2016