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Janssen
PHARMACEUTICAL COMPANIES
of Johnson & Johnson

24 May 2016

Professor Helena Teede
President
Endocrine Society of Australia
145 Macquarie Street
SYDNEY NSW 2000

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

Dear Professor Teede

Janssen-Cilag Pty Ltd ('Janssen'), in consultation with the Therapeutic Goods Administration (TGA), would like to inform you of new important safety information relating to INVOKANA® (canagliflozin).

Please find attached a letter providing this new important safety information relating to INVOKANA®.

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 TGA (at http://www.tga.gov.au/safety/problem-medicine.htm) and/or Janssen's Medical Information Department.

If you have further questions or require additional information, please contact Janssen Medical Information on 1800 226 334 or medinfo@janau.jnj.com

Sincerely

RBriffa

Renee Briffa B.Pharm
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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'), in consultation with the Therapeutic Goods Administration (TGA), 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 TGA (at http://www.tga.gov.au/safety/problem-medicine.htm) and/or Janssen's Medical Information Department.

Please refer to the Product Information (PI) for complete prescribing information on INVOKANA®, available from the TGA (at https://www.ebs.tga.gov.au/) or Janssen Medical Information Department or at http://www.janssen.com.au/invokana_pi.

If you have further questions or require additional information, please contact Janssen Medical Information on 1800 226 334 or medinfo@janau.jnj.com.

Sincerely

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

References:

1. INVOKANA (canagliflozin) Product Information. 26 Feb 2016