HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

SGLT2 inhibitors and risk of lower limb amputation (mainly toe)

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its review of the risk of lower limb amputation (mainly affecting the toes) associated with sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin and empagliflozin), which are indicated in adults for the treatment of Type 2 diabetes, as monotherapy or in combination with other diabetes medicines.

In May 2016, healthcare professionals were informed, via a Direct Healthcare Professional Communication (DHPC), of a two-fold higher incidence of lower limb amputation (primarily of the toe) which had been seen in the ongoing long-term CANVAS clinical trial with canagliflozin. An increased risk has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin, however data available to date are limited. As all SGLT2 inhibitors share a similar mechanism of action and, as the mechanism leading to an increased amputation risk, or an underlying cause specific to canagliflozin-containing medicines could not be established, a class effect could not be excluded. Therefore, the PRAC review encompassed all of the authorised products within the SGLT2 inhibitor class.

During the recently concluded PRAC review, interim data from two ongoing long-term clinical trials involving patients with or at high cardiovascular risk (CANVAS and CANVAS-R) were considered, along with all related available data from finalised and other ongoing clinical trials and reports from post-marketing surveillance available from the marketing authorisation holders (MAHs) of all authorised SGLT2 containing medicinal products. On the basis of the currently available data, the PRAC concluded that treatment with canagliflozin may contribute to an increased risk of amputation of the lower limb, mainly affecting the toes, but considered that a possible class effect cannot be currently excluded. While further specific risk factors (apart from general risk factors) for amputation events could not be identified, the PRAC recommended that patients should continue to receive advice on routine preventative foot care and maintaining adequate hydration, as general advice to prevent amputation. The product information of all SGLT2 inhibitors will be updated to include a warning of the risk of lower limb amputation (primarily of the toes), highlighting to healthcare professionals and patients the importance of routine preventative foot care. Lower limb amputation will also be included as an uncommon adverse reaction in the product information for canagliflozin-containing products. The warning for canagliflozin-containing products will also highlight carefully monitoring patients with a higher risk for amputation events and that, in patients developing amputation preceding events such as infection or skin ulceration, consideration may be given to discontinuing treatment.

The PRAC concluded that the benefit-risk balance of SGLT2 inhibitor-containing products remains favourable, subject to these amendments to the product information. The PRAC recommendations were endorsed by the Committee for Medicinal Products for Human Use (CHMP) and will now be passed to the European Commission for a final, legally binding, decision which will be applicable in all Member States.

Advice to Healthcare Professionals

- All patients taking an SGLT2 inhibitor should be counselled on the importance of routine preventative foot care.
- Patients taking canagliflozin, with risk factors for amputation events, such as previous amputation, existing peripheral vascular disease or neuropathy, should be monitored carefully and counselled on the importance of maintaining adequate hydration.
- Patients should be counselled to notify their healthcare professional if they develop ulceration, discolouration, new pain or tenderness in their feet.
- Treatment discontinuation should be considered for patients taking canagliflozin who develop amputation preceding events, for example, lower extremity skin ulcer, infection, osteomyelitis or gangrene.
- Any suspected adverse reactions should be reported to the HPRA through the available options (www.hpra.ie).

Key Message

- An increase in cases of lower limb amputation, primarily affecting the toes, has been observed in patients taking the SGLT2 inhibitor canagliflozin compared with those taking placebo in two ongoing clinical trials. While available data to date is limited, a risk cannot be excluded for the other medicines within the same class, dapagliflozin and empagliflozin.
- Patients should be advised on routine preventative foot care and maintaining adequate hydration as a general advice to prevent amputation.
- Therapy discontinuation should be considered if patients taking canagliflozin develop significant foot complications such as infection or ulcers.
- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these products will be updated shortly.

SGLT2 inhibitor-containing products include Forxiga, Xigduo, Jardiance, Synjardy, Edistride, Ebymect, Invokana and Vokanamet. Further details are available on www.hpra.ie and www.ema.europa.eu