Information on potential risk of toe amputation with SGLT2 inhibitors to be included in the prescribing information

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Information on sodium-glucose co-transporter-2 (SGLT2) inhibitors

Canagliflozin, dapagliflozin and empagliflozin are type 2 diabetes mellitus medicines of the class sodium-glucose co-transporter-2 (SGLT2) inhibitors.

- SGLT2 inhibitors work by blocking a protein in the kidneys called SGLT2. This protein absorbs glucose back from the urine into the bloodstream as the blood is filtered in the kidneys.
- Through the blocking of SGLT2, these medicines cause more glucose to be lost in the urine, thereby reducing the levels of glucose in the blood.
- In Europe SGLT2 containing medicines and SGLT2 combination products are authorised under the following trade names: Ebymect (dapagliflozin / metformin), Edistride (dapagliflozin), Forxiga (dapagliflozin), Invokana (canagliflozin), Jardiance (empagliflozin), Synjardy (empagliflozin / metformin), Vokanamet (canagliflozin / metformin) and Xigduo (dapagliflozin / metformin).

Invokana, Forxiga and Jardiance are marketed in Malta through the centralised procedure.

Potential risk of toe amputation with SGLT2 inhibitors to be included in the prescribing information - Diabetes patients reminded of importance of preventative foot care

The European Medicines Agency (EMA) has concluded its review of SGLT2 inhibitors. The potential increased risk of lower limb amputation (mostly affecting the toes) in patients taking the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes will be included in the prescribing information.

- The review of SGLT2 inhibitors (previously canagliflozin, refer to circular P17/2016) was prompted by an increase in lower limb amputations (mostly affecting the toes) in patients taking canagliflozin in two clinical trials, CANVAS and CANVAS-R. The studies, which are still ongoing, involved patients at high risk of heart problems and compared canagliflozin with placebo (a dummy treatment).
- All patients with diabetes (especially those with poorly controlled diabetes and problems with the heart and blood vessels) are at higher risk of infection and ulcers (sores) which can lead to

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amputations. The mechanism by which canagliflozin may increase the risk of amputation is still unclear.

- An increase in lower limb amputations has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin. However, the data available to date is limited and the risk may also apply to these other medicines. Further data is expected from ongoing studies with canagliflozin, dapagliflozin and empagliflozin.
- A warning of the potential increased risk of toe amputation will be included in the prescribing information for these medicines. For canagliflozin, the prescribing information will also list lower limb amputation as an uncommon side effect (occurring in between 1 and 10 patients in 1,000). Doctors may consider stopping treatment with canagliflozin if patients develop significant foot complications such as infection or skin ulcers.
- Patients taking these medicines are reminded to check their feet regularly and follow their doctor's advice on routine preventative foot care. They should also tell their doctor if they notice any wounds or discoloration, or if their feet are tender or painful.

The review of SGLT2 inhibitors was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations have now been endorsed by the Committee for Medicinal Products for Human Use (CHMP), and will be sent to the European Commission for a final legally-binding decision valid throughout the EU.

In Malta

Information for healthcare professionals

- An increase in lower limb amputation (mostly affecting the toes) has been observed in two long-term clinical trials, CANVAS and CANVAS-R, in patients taking canagliflozin compared with those taking placebo. The studies, which are still ongoing, involved patients at high cardiovascular risk.
- Although an increase in amputations has not been seen in studies with other SGLT2 inhibitors, dapagliflozin and empagliflozin, data available to date is limited and the risk may also apply to these other medicines.
- The underlying mechanism by which canagliflozin may increase the risk of amputation has not been established and no risk factors apart from general risk factors for amputation have been identified.
- As a precaution, patients taking an SGLT2-inhibitor should be counselled about the importance of routine preventative foot care.

- For canagliflozin, consideration should also be given to carefully monitoring patients at higher risk of amputation and counselling them about the importance of maintaining adequate hydration.
- Consideration may be given to stopping treatment with canagliflozin in patients who develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

More information on SGLT2 inhibitors can be found on EMA's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

Information for patients

- The diabetes medicine canagliflozin may increase the risk of lower limb amputation (mostly affecting the toes).
- The risk of lower limb amputation with canagliflozin may also apply to other diabetes medicines in the same class, dapagliflozin and empagliflozin.
- All patients with diabetes are at increased risk of infection and sores which can lead to amputations. It is currently not known how canagliflozin may increase the risk of toe amputation.
- If you are taking medicines containing canagliflozin, dapagliflozin and empagliflozin to treat your type 2 diabetes, it is particularly important that you check your feet regularly and follow your doctor's advice on routine preventative foot care and adequate hydration.
- Tell your doctor about any wounds or discoloration, or if your feet are tender or painful.
- If you have any questions or concerns about your treatment, speak to your doctor, pharmacist or nurse.

For more information on this issue refer to the EMA press release

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on SGLT2 inhibitors. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form (available from: **http://www.medicinesauthority.gov.mt/adrportal**) and sent by mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or email to **postlicensing.medicinesauthority@gov.mt** or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

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