

**Product Information as approved by the CHMP on 23 February 2017, pending endorsement  
by the European Commission**

**Amendments to relevant sections of the summary of product characteristics  
and package leaflet**

*Note:* These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

For Invokana, Vokanamet, Forxiga, Edistride, Xigduo, Ebymect, Jardiance and Synjardy, the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below

## Summary of product characteristics

### Canagliflozin

#### 4.4 Special warnings and precautions for use

A warning should be added as follows:

##### Lower Limb Amputations

In ongoing, long-term clinical studies of canagliflozin in T2DM patients with cardiovascular disease (CVD) or at high risk for CVD, an increase in cases of lower limb amputation (primarily of the toe) has been observed in patients treated with canagliflozin.

As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown. However, as precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with canagliflozin in patients that develop events preceding amputation such as lower-extremity skin ulcer, infection, osteomyelitis or [gangrene](#).

#### 4.8 Undesirable effects

The following adverse reaction(s) should be added under the SOC Surgical and medical procedures with a frequency uncommon as follows:

##### 4.8 Undesirable effects

System organ class	Adverse reaction
Frequency	
Surgical and medical procedures	
uncommon	lower limb amputations (mainly of the toe) especially in patients at high risk for heart disease

## Package leaflet

### Section 2: What you need to know before you take canagliflozin

#### Warnings and precautions

It is important to check your feet regularly and adhere to any other advice regarding foot care and adequate hydration given by your health care professional. You should notify your doctor immediately if you notice any wounds or discolouration, or if you experience any tenderness or pain in your feet. Some studies indicate that taking canagliflozin may have contributed to the risk of lower limb amputation (mainly toe amputations).

## **Section 4: Possible side effects**

Other side effects:

Uncommon (may affect up to 1 in 100 people)

- lower limb amputations (mainly of the toe) especially if you are at high risk of heart disease

## **Dapagliflozin**

### **4.4 Special warnings and precautions for use**

A warning should be added as follows:

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

## **Package leaflet**

### **Section 2: What you need to know before you take dapagliflozin**

Warnings and precautions

Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

## **Empagliflozin**

### **4.4 Special warnings and precautions for use**

A warning should be added as follows:

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

## **Package leaflet**

### **Section 2: What you need to know before you take dapagliflozin**

Warnings and precautions

Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.