ADDENDUM TO NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004 (procedure number EMEA/H/A-20/1442)

This is an addendum to the 15 April 2016 notification by the European Commission of a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) concerning the following medicinal products:

Product(s) Name(s)	INVOKANA (canagliflozin) VOKANAMET (canagliflozin / metformin) EDISTRIDE (dapagliflozin) FORXIGA (dapagliflozin) XIGDUO (dapagliflozin / metformin) EBYMECT (dapagliflozin / metformin) JARDIANCE (empagliflozin) SYNJARDY (empagliflozin / metformin)
Active Substance(s)	See above
Pharmaceutical form(s)	All pharmaceutical forms
Strength(s)	All strengths
Route(s) of administration	All routes of administration
Marketing Authorisation Holder(s)	Janssen- Cilag International AstraZeneca AB Boehringer Ingelheim

On 15 April 2016, the European Commission requested the Agency to assess the data available concerning the potential risk of lower limb amputation with canagliflozin containing medicines and their impact on the benefit-risk balance and to give its opinion under Article 20 of Regulation (EC) No 726/2004 on whether regulatory action with regard to the marketing authorisation for these products is necessary.

It was noted in the notification that all sodium-glucose co-transporter 2 (SGLT2) inhibitors share the same mechanism of action and that the mechanism behind this potential risk is unknown, so the Pharmacovigilance Risk Assessment Committee (PRAC) was invited to consider if it was necessary to extend the review to the other SGLT2 inhibitors (dapagliflozin and empagliflozin-containing medicines).

Having considered the available data the PRAC is of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk specific to canaglifozin-containing medicines and different from the other members of the class of medicines. Data on amputation events from clinical trials and post-marketing surveillance for dapagliflozin and empagliflozin-containing medicines are either not available to the same extent as canagliflozin-containing medicines or has some limitations, therefore PRAC considered that a class effect cannot be excluded.

In view of the above, the European Commission extends the scope of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 to allow a review of data from the class of SLG2-inhibitors and requests the Agency to assess the risk of amputation and their impact on the benefit-risk balance for the centrally authorised medicinal products: Invokana (canagliflozin), Vokanamet (canagliflozin/metformin), Edistride (dapagliflozin), Forxiga (dapagliflozin), Xigduo (dapagliflozin/metformin), Ebymect (dapagliflozin/metformin), Jardiance (empagliflozin) and Synjardy (empagliflozin/metformin). The European Commission requests the EMA to give its opinion by 31 March 2017 on whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

Signed [redacted] Date 6.7.2016

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